#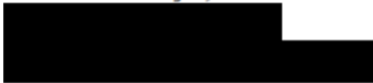 A PHASE 3 OPEN-LABEL RANDOMIZED STUDY OF QUIZARTINIB MONOTHERAPY VERSUS SALVAGE CHEMOTHERAPY IN SUBJECTS WITH FLT3-ITD POSITIVE ACUTE MYELOID LEUKEMIA (AML) REFRACTORY TO OR RELAPSED AFTER FIRST-LINE TREATMENT WITH OR WITHOUT HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) CONSOLIDATION

Product	Quizartinib
Protocol Number	AC220-007
Study Phase	3
Indication	Refractory or relapsed FLT3-ITD(+) acute myeloid leukemia
IND	74,552
EudraCT No.	2013-004890-28
Original Version	18 November 2013
Amendment 1	24 December 2013
Amendment 2	26 May 2015
Amendment 3	06 October 2015
Amendment 3.1	19 November 2015
Amendment 4	04 May 2016
Amendment 5	15 August 2016
Amendment 6	30 June 2017
Sponsor	Daiichi Sankyo, Inc. 211 Mt. Airy Road Basking Ridge, NJ 07920-2311 United States
Medical Monitor	▉▉▉▉▉▉▉▉ Daiichi Sankyo, Inc. ▉▉▉▉▉▉▉▉

INVESTIGATOR'S STATEMENT

I have received and completely reviewed the following protocol (AC220-007, Global Amendment 6.0, dated 30 Jun 2017), including all appendices:

As Principal Investigator, I understand and agree to conduct this clinical study as described and will comply with the ethical and regulatory considerations delineated herein.

Study Title

A Phase 3 Open-Label Randomized Study of Quizartinib Monotherapy Versus Salvage Chemotherapy in Subjects with FLT3-ITD Positive Acute Myeloid Leukemia (AML) Refractory To or Relapsed After First-line Treatment With or Without Hematopoietic Stem Cell Transplantation (HSCT) Consolidation

PRINCIPAL INVESTIGATOR SIGNATURE AND CONTACT INFORMATION

Principal Investigator
(signature)

_____

Principal Investigator
(please print)

_____

Date of Signature

_____

Institution/Affiliation

_____

City, State

_____

Country

_____

Signature on this page assures the Sponsor that, to the best of the Principal Investigator's knowledge, the affiliated IRB/Ethics Committee operates in accordance with the US Code of Federal Regulations and/or other local regulations, and that the Investigator understands, and agrees to comply with, all US FDA regulatory obligations and other local regulations, and ICH Guidelines for Good Clinical Practice (GCP), while conducting this clinical study.

Once signed, the original form should be detached from the protocol and returned to the Sponsor.

(Please retain a copy for your study files)

STUDY SYNOPSIS

NAME OF SPONSOR	NAME OF FINISHED PRODUCT	NAME OF ACTIVE INGREDIENT
Daiichi Sankyo, Inc. 211 Mt. Airy Road Basking Ridge, NJ 07920-2311 United States	Quizartinib tablets	Quizartinib

TITLE: A Phase 3 Open-Label Randomized Study of Quizartinib Monotherapy Versus Salvage Chemotherapy in Subjects with FLT3-ITD Positive Acute Myeloid Leukemia (AML) Refractory To or Relapsed After First-line Treatment With or Without Hematopoietic Stem Cell Transplantation (HSCT) Consolidation

INDICATION: Relapsed or refractory FLT3-ITD(+) AML

STUDY PHASE: 3

STUDY CENTERS: Approximately 150 centers globally

NUMBER OF SUBJECTS PLANNED: Approximately 363 subjects will be randomized.

STUDY DURATION: Approximately 36 months

STUDY OBJECTIVES

The primary objective of the study is to determine whether quizartinib monotherapy prolongs overall survival (OS) compared to salvage chemotherapy in subjects with FLT3-ITD positive AML who are refractory to or have relapsed within 6 months, after first-line AML therapy.

The secondary objective is to determine event-free survival (EFS) with quizartinib versus salvage chemotherapy.

Exploratory objectives are:

- to compare the composite complete remission (CRc = complete remission [CR] + complete remission with incomplete platelet recovery [CRp] + complete remission with incomplete hematologic recovery [CRi]) rate

- to compare the complete remission (CR) rate

- to compare the duration of composite complete remission (CRc)

- to compare the duration of complete remission (CR)

- to determine leukemia-free survival (LFS)

- to compare the transplantation rate

- to determine the QTc prolonging effects of quizartinib in relation to plasma drug concentrations

- to determine the pharmacokinetics (PK) of quizartinib and its active metabolite, AC886

- to determine the exposure-response relationship

- to determine resource utilization in this study population

- to identify AML-associated mutations and their frequencies

- pharmacogenomic and pharmacoproteomic determinations

STUDY DESIGN

This is a Phase 3, randomized, open-label, 2-arm study to compare the effect of quizartinib monotherapy and salvage chemotherapy on OS in subjects with FLT3-ITD (+) AML that is refractory or relapsed within 6 months, after first-line therapy with or without consolidating hematopoietic stem cell transplantation (HSCT).

The study will utilize a group sequential design with 1 interim analysis at 0.5 information fraction (ie, approximately 50% of planned number of events). The target sample size will be approximately 363 subjects, randomized in a 2:1 ratio to receive quizartinib monotherapy (242 subjects) or salvage chemotherapy (121 subjects). One formal interim analysis will be performed by an independent statistical analysis center (SAC) and evaluated by an independent data monitoring committee (DMC), according to statistical procedures defined a priori. Based on the results of the interim analysis, the DMC may recommend that the study be terminated early for futility or for efficacy, or continue as planned. The tasks performed by the SAC and DMC are described in the DMC charter and Interim Analysis Plan.

Prior to randomization, the Investigator will pre-select a salvage chemotherapy regimen for each subject; options include low dose cytarabine (LoDAC); mitoxantrone, etoposide, and intermediate-dose cytarabine (MEC); or fludarabine, cytarabine, and granulocyte colony stimulating factor (G-CSF) with idarubicin (FLAG-IDA).

Screening

During the 14 day screening period, subjects will undergo medical history evaluation, physical examination, vital sign determination, Eastern Cooperative Oncology Group (ECOG) performance status assessment, chest X-ray, concomitant medication assessment, blood and urine sampling for laboratory tests, ECG monitoring, and bone marrow aspiration/biopsy to confirm FLT3-ITD status and confirm diagnosis. Subjects will undergo multiple gated acquisition (MUGA) scans or echocardiography (ECHO).

STUDY POPULATION

Inclusion Criteria

To be able to participate in this study, candidates must meet the following criteria at screening or other specified time point:

1. Provision of written informed consent approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) with privacy language in accordance with national regulations [eg, Health Insurance Portability and Accountability Act (HIPAA) authorization for US sites] prior to any study-related procedures, including withdrawal of prohibited medications if applicable.

2. Age ≥18 years or the minimum legal adult age (whichever is greater) at the time of informed consent.

3. Morphologically documented primary AML or AML secondary to myelodysplastic syndrome (MDS), as defined by World Health Organization criteria, as determined by pathology review at the study site.

4. In first relapse (with duration of remission of 6 months or less) or refractory after prior therapy, with or without HSCT. Induction therapy must have included at least 1 cycle of an anthracycline/mitoxantrone containing induction block at a standard dose.

   - Refractory is defined as:

     – After 1 cycle, a reduction in bone marrow blasts of less than 50% and failure to achieve a CR, CRp, or CRi.

     – After 2 cycles, lack of achievement of CR, CRp, or CRi

   - First relapse (with duration of remission of 6 months or less) is defined as:

     – Achievement of CR, CRi, or CRp, as defined by 2003 International Working Group criteria after initial AML therapy with or without consolidation or maintenance, and with or without HSCT.

     – Duration of CR, CRi or CRp is measured from the date of the bone marrow assessment which confirmed response or the date of allogeneic transplantation to the date of the bone marrow assessment that identified relapse or the appearance of peripheral blasts.

5. Presence of the FLT3-ITD activating mutation in bone marrow or peripheral blood (allelic ratio as determined by a central laboratory with a cutoff of $\geq$3% FLT3-ITD/total FLT3). If a specimen has been sent for FLT3-ITD testing at the central laboratory but the subject requires treatment for AML before the central FLT3-ITD test result is available, a local test result may be acceptable for randomization after consultation with the Medical Monitor.

6. Eligibility for pre-selected salvage chemotherapy, according to the Investigator's assessment.

7. ECOG performance score 0-2.

8. Discontinuation of prior AML treatment before the start of study treatment (except hydroxyurea or other treatment to control leukocytosis) for at least 2 weeks for cytotoxic agents, or for at least 5 half-lives for non-cytotoxic agents.

9. Serum creatinine $\leq$1.5$\times$upper limit of normal (ULN), or glomerular filtration rate >25 mL/min, as calculated with the Cockcroft-Gault formula.

10. Serum potassium, magnesium, and calcium (serum calcium corrected for hypoalbuminemia) within institutional normal limits. Subjects with electrolytes outside the normal range will be eligible if these values are corrected upon retesting following any necessary supplementation.

11. Total serum bilirubin $\leq$1.5$\times$ULN.

12. Serum aspartate transaminase (AST) and/or alanine transaminase (ALT) $\leq$2.5$\times$ULN.

Exclusion Criteria

Candidates will be excluded from study entry if any of the following criteria are met at screening or other specified time point:

1. Acute promyelocytic leukemia (AML subtype M3).

2. AML secondary to prior chemotherapy for other neoplasms, except AML secondary to prior MDS.

3. History of another malignancy, unless the candidate has been disease-free for at least 5 years.

   - Candidates with treated non-melanoma skin cancer, carcinoma in situ, or cervical intraepithelial neoplasia are eligible regardless of the time spent disease-free, if they have completed definitive treatment.

   - Candidates with organ-confined prostate cancer, with no evidence of recurrent or progressive disease, are eligible if hormonal therapy has been begun, or if the tumor has been surgically removed or treated with definitive radiotherapy.

4. Persistent, clinically significant > Grade 1 non-hematologic toxicity from prior AML therapy.

5. Clinically significant GVHD or GVHD requiring initiation of treatment or treatment escalation within 21 days, and/or > Grade 1 persistent or clinically significant non-hematologic toxicity related to HSCT.

6. History of or current, central nervous system involvement with AML.

7. Clinically significant coagulation abnormality, such as disseminated intravascular coagulation.

8. Prior treatment with quizartinib or participated in a prior quizartinib study.

9. Prior treatment with a FLT3 targeted therapy including sorafenib or investigational FLT3 inhibitors (not including the multi-kinase inhibitor, midostaurin).

10. Major surgery within 4 weeks prior to screening.

11. Radiation therapy within 4 weeks prior to screening.

12. Uncontrolled or significant cardiovascular disease, including:

    - QT interval corrected using Fridericia's formula (QTcF) interval >450 msec (average of triplicate determinations).

    - Subject has bradycardia of less than 50 BPM (as determined by central reading) unless the subject has a pacemaker.

    - Diagnosed or suspected long QT syndrome, or known family history of long QT syndrome.

    - History of clinically relevant ventricular arrhythmias, such as ventricular

tachycardia, ventricular fibrillation, or torsade de pointes.

- History of second or third degree heart block. Candidates with a history of heart block may be eligible if they currently have pacemakers, and have no history of fainting or clinically relevant arrhythmia with pacemakers.

- Myocardial infarction within 6 months prior to screening.

- Uncontrolled angina pectoris within 6 months prior to screening.

- New York Heart Association (NYHA) Class 3 or 4 congestive heart failure.

- Left ventricular ejection fraction (LVEF) $\leq$45 % or institutional lower limit of normal.

- Uncontrolled hypertension.

- Complete left or right bundle branch block.

13. Active infection not well controlled by antibacterial, antifungal, and/or antiviral therapy.

14. Known infection with human immunodeficiency virus, or active hepatitis B or C, or other active clinically relevant liver disease.

15. Unwillingness to receive infusion of blood products according to the protocol.

16. In a man whose sexual partner is a woman of childbearing potential, unwillingness or inability of the man or woman to use a highly effective contraceptive method for the entire study treatment period and for at least 3 months after study treatment completion.

- Male subjects must not freeze or donate sperm starting at Screening and throughout the study period and 105 days after the final study drug administration.

17. In a heterosexually active woman of childbearing potential, unwillingness or inability to use a highly effective contraceptive method for the entire study treatment period and for at least 3 months after study treatment completion. Additionally, for women randomized to chemotherapy, unwillingness to adhere to the restrictions in the respective locally established guidelines and local approved label (prescribing information, Summary of Product Characteristics, or US product insert) from the manufacturer and the Patient Information Leaflet (package insert) as instructed by the Investigator.

- Women are not regarded as of childbearing potential if they are post-menopausal (at least 2 years without menses) or are surgically sterile (at least 1 month before study).

- Highly effective contraception methods include: hormonal methods associated with inhibition of ovulation, intra-uterine device; surgical sterilization (including partner's vasectomy) or sexual abstinence if this is the preferred and usual lifestyle of the subject.

- Female subjects must not donate or retrieve, for their own use, ova from the time of Screening and throughout the study treatment period, and for 12 weeks after the

final study drug administration.

18. Pregnancy

19. Female subjects must agree not to breastfeed from the time of Screening and throughout the study period, and for 25 days after the final study drug administration.

20. Medical condition, serious intercurrent illness, or other circumstance that, in the Investigator's judgment, could jeopardize the candidate's safety as a study subject, or that could interfere with study objectives.

21. For subjects in the UK only: Refusal of permission to allow the subject's General Practitioner to be notified of their participation in the study.

STUDY TREATMENT

Quizartinib

For subjects randomized to quizartinib the starting dose will be 30 mg/day unless the subject is receiving concurrent therapy with a strong CYP3A4 inhibitor, in which case the starting dose will be 20 mg/day. The dose will be taken in the morning with or without food over continuous 28-day cycles. 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, no replacement dose should be given.

CYCLE 1 DAY 16

For subjects not taking a strong CYP3A4 inhibitor the dose of quizartinib will be increased from 30 to 60 mg/day starting on Day 16 based on the following criteria:

- The subject's average QTcF, based on triplicate reading, must be ≤ 450 msec on and before Day 15.

For subjects taking a strong CYP3A4 inhibitor, the dose of quizartinib will be increased from 20 mg/day to 30 mg/day providing they meet the above QTcF requirements.

CYCLE 2 DAY 1

Subjects who fail to achieve a CR, CRp, or CRi as defined in Section 7.2 after at least one 28-day cycle of therapy may undergo dose escalation if the following criteria are met:

- Subject has not had dose interruption or dose reduction for a Grade 3 or higher, non-hematologic, and related adverse event.

- No increase in QTcF more than 60 msec above baseline.

- The subject must not have aplastic bone marrow at the time of the proposed dose escalation.

In addition, subjects who achieved a response [CR, CRi, CRp or partial remission (PR)] at any time, and who have subsequently relapsed, may undergo dose escalation provided they meet the same criteria outlined above.

For subjects not taking a strong CYP3A4 inhibitor the dose of quizartinib will be increased to 60 mg/day.

For subjects taking a strong CYP3A4 inhibitor, the dose of quizartinib will be increased to 30 mg/day providing they meet the above requirements.

Following dose escalation, triplicate ECG determinations should be performed at least once weekly for 2 weeks to monitor QTcF prolongation.

If any of the following criteria are met, the quizartinib dose will be reduced stepwise from 60 mg/day to 30 mg/day or from 30 mg/ day to 20 mg/day or discontinued. No further dose reductions below 20 mg/day will be allowed.

- **QTcF prolongation**
  - Grade 2 (QTcF average of triplicate readings > 480 msec) (All toxicity grades according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.03)
    - The dose will be reduced without interruption.
    - If 20 mg/day is the current dose, dosing will be interrupted for up to 14 days. If QTcF returns to within 30 msec of baseline or ≤ 450 msec within 14 days, treatment may be resumed at 20 mg/day.
  - Grade 3 (QTcF average of triplicate readings > 500 msec)
    - Dosing will be interrupted for up to 14 days. If QTcF returns to within 30 msec of baseline or ≤ 450 msec within 14 days, treatment may be resumed at a reduced dose.
    - If 20 mg/day is the current dose, dosing will be interrupted for up to 14 days. If QTcF returns to within 30 msec of baseline or ≤ 450 msec within 14 days, treatment may be resumed at 20 mg/day. If Grade 3 event returns, treatment will be discontinued.
  - Grade 4 (QTcF > 500 msec or > 60 msec change from baseline, and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)
    - Treatment will be discontinued.

- **Non-hematologic toxicity**
  - Grade 3 or 4 related to quizartinib and persisting >48 hours without improvement to ≤ Grade 2
    - Dosing will be interrupted for up to 14 days.
    - If toxicity improves to ≤ Grade 1 within 14 days, treatment may be resumed at the reduced dose.

- **Myelosuppression**
  - In a subject with CRp or CRi, the dose may be reduced at the Investigator's discretion if:
    - The subject has been treated for a minimum of 2 cycles.
    - Platelet count is <100 × 10^9/L and absolute neutrophil count (ANC) is ≤ 1000 × 10^9/L.

- Marrow blasts < 5%.
- There is no evidence of extramedullary disease.

- **Initiation of concomitant treatment with a strong CYP3A4 inhibitor**
  - The dose will be reduced from either 60 mg/day to 30 mg/day or from 30 mg/day to 20 mg/day.
  - A subject taking a strong CYP3A4 inhibitor at time of randomization will initiate quizartinib administration at 20 mg/day.

In subjects receiving a reduced dose of quizartinib, the dose may be re-escalated stepwise from 20 mg to 30 mg to 60 mg, except following Grade 3 QTcF prolongation. If the dose was reduced due to toxicity, all events responsible for dose reduction must have resolved to $\leq$ Grade 1. If the dose was reduced due to administration of a strong CYP3A4 inhibitor, the prior dose can be resumed when the inhibitor is withdrawn.

If a subject undergoes HSCT, quizartinib should be discontinued 7 days before the start of a conditioning regimen. For a subject who was randomized to and received quizartinib, treatment with quizartinib may be resumed at 30 to 100 days after the transplant. Quizartinib may be restarted if:

- Subject has an ANC > 1 x 10^9/L and platelet count > 50×10^9/L without platelet transfusion support within 1 week, or a platelet count > 25×10^9/L without platelet transfusion support within 2 weeks prior to first dose.

- Subject does not have (1) active acute, or $\geq$ Grade 3 graft versus host disease (GVHD) or (2) active GVHD therapy (not prophylaxis) initiation in the preceding 21 days.

Follow-up

After study treatment is discontinued, subjects will be followed for 30 days for safety. Assessment of best response to chemotherapy should be conducted at Day 29 ($\pm$14 days) or prior to starting subsequent AML therapy. Subjects will then enter long term follow-up every 3 months for collection of information on subsequent AML treatment, remission status, and survival, including the cause and date of death.

Salvage Chemotherapy

The Investigator will pre-select the specific salvage chemotherapy regimen before randomization of each subject. All salvage chemotherapy will be administered during 28-day cycles. The start of Cycle 2 (MEC, FLAG-IDA, or LoDAC) and subsequent cycles (LoDAC) may be delayed for up to 14 days to allow for recovery from toxicity. Dose reductions are allowed for toxicity but must be documented in the source record.

Low Dose Cytarabine (LoDAC)

Cytarabine (20 mg) will be administered twice daily by subcutaneous injection for 10 days (Days 1 through 10) over continuous 28-day cycles. A delay of up to 14 days between cycles is allowed for recovery from toxicity.

MEC Chemotherapy

- Mitoxantrone (8 mg/m^2/day) will be administered by 5 minute intravenous (IV)

injection for 5 days (Days 1 through 5).

- Etoposide (100 mg/m^2/day) will be administered by 1 hour IV infusion immediately after mitoxantrone for 5 days (Days 1 through 5).

- Cytarabine (1000 mg/m^2/day) will be administered by 1 hour IV infusion immediately after etoposide for 5 days (Days 1 through 5).

FLAG-IDA Chemotherapy

- G-CSF (300 μg/m^2/day) will be administered by 2 hour IV infusion for 5 days (Days 1 through 5) or alternatively, G-CSF (5 μg/kg/day) may be administered SC for 5 days (Days 1 through 5). Additional G-CSF is recommended 7 days after the completion of chemotherapy, until ANC is >0.5×10^9/L.

- Fludarabine (30 mg/m^2/day) will be administered by 30 minute IV infusion for 5 days (Days 2 through 6).

- Cytarabine (2000 mg/m^2/day) will be administered by 4 hour IV infusion, beginning 4 hours after the fludarabine infusion, for 5 days (Days 2 through 6).

- Idarubicin (10 mg/m^2/day) will be administered over 5 to 10 minutes in a fast-running saline drip for 3 days (Days 2 through 4).

In subjects receiving quizartinib or LoDAC, treatment should continue until there is no longer clinical benefit from therapy, or until unacceptable toxicity occurs. Subjects that receive either quizartinib or LoDAC will be assessed for response on Day 1 of Cycle 2 and Day 1 of Cycle 3 as well as on Day 1 of each subsequent cycle unless the subject has already achieved CR, CRp, or CRi. In that event, bone marrow testing will be repeated after every 3 subsequent cycles, unless there is evidence of relapse.

Subjects receiving MEC or FLAG-IDA will receive 1 cycle of therapy and be assessed for response at Day 29 (± 14 days). Salvage chemotherapy should be given as 28 day cycles, although cycles may be delayed for recovery from toxicity or blood count recovery for up to 14 days.

Subjects achieving complete remission (CR), complete remission with incomplete hematologic recovery (CRi), or complete remission with incomplete platelet recovery (CRp) (per Investigator assessment), may receive a second cycle of the same therapy at the Investigator's discretion. Treatment should be discontinued if there is no evidence of response or progressive disease (PD). For subjects who demonstrate some level of clinical benefit but do not achieve a remission, the decision on additional treatment is at the Investigator's discretion.

CONCOMITANT MEDICATIONS

For all subjects (quizartinib and salvage chemotherapy): Administration of other antineoplastic agents during the study period is prohibited with the exception of hydroxyurea which is allowed for up to 14 days prior to or for up to 4 days concomitantly with quizartinib or salvage chemotherapy to control the peripheral blast count, up to a maximum dose of 5 g/day.

In subjects receiving quizartinib, concomitant medications that prolong the QT/QTc interval are prohibited except when regarded by the Investigator as essential for subject care. The use of a strong CYP3A4 inhibitor should be avoided if possible, but is not prohibited although

quizartinib dose adjustments are required. Weak or moderate CYP3A4 inhibitors, such as fluconazole may be used without a quizartinib dose reduction.

Concomitant strong or moderate CYP3A4 inducers are prohibited.

If quizartinib is co-administered with drugs that inhibit P-gp, increased concentrations of quizartinib are possible and caution should be exercised. The co-administration of P-gp inhibitors and inducers with quizartinib should be avoided if possible. 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.

STUDY VARIABLES

Primary Efficacy Variable

The primary efficacy variable is OS, defined as the time from randomization until death from any cause.

Secondary Efficacy Variable

The secondary variable is EFS, the time from randomization until documented refractory disease, relapse after CRc, or death from any cause, whichever is observed first.

Additional Efficacy Variables

- Leukemia-free survival is the time from the first documented response (CR, CRp, or CRi) until documented relapse or death from any cause.

- Composite complete remission (CRc) rate is the percentage of subjects achieving a best response of CR, CRp, or CRi.

- Complete remission (CR) rate is the percentage of subjects achieving a best response of CR.

- Duration of composite complete remission (CRc) is the time from the first documented CRc (CR + CRi + CRp) until documented relapse.

- Duration of complete remission (CR) is the time from the first documented complete remission (CR) until documented relapse.

- Transplantation rate (bridge to transplant) is the percentage of subjects undergoing HSCT directly following protocol-specified treatment with no intervening AML therapy.

Safety Variables

- Adverse events

- Vital signs

- Hematology, serum chemistry, and urinalysis results

- Physical examination results

- ECG results

- ECOG performance scores

Pharmacokinetic and Exposure-response Variables

- Pharmacokinetics of quizartinib and its active metabolite, AC886
- Concentration-QTcF Relationship
- Other exposure-response relationships with efficacy or safety variables

Genomic and Proteomic Variables

- FLT3-ITD status and allelic ratio
- Mutations in the kinase and juxtamembrane domains of FLT3-ITD and other mutations known to be associated with AML, determined with bone marrow or whole blood samples
- Pharmacogenomics
- Pharmacoproteomic evaluations

Pharmacoeconomic Variables

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

STATISTICAL METHODS

Sample Size Determination

Calculation of sample size is based on comparison of OS, the primary efficacy endpoint, in the 2 treatment groups (quizartinib and salvage chemotherapy) at a 2-sided significance level of 0.05, assuming that median survival is 3.9 months in the salvage chemotherapy group with an increase to 6 months, in the quizartinib group (hazard ratio 0.65). A total of 280 events (deaths) are necessary to meet a power requirement of 90%, given an interim analysis planned at 140 events (deaths) with O'Brian-Fleming boundary for superior efficacy and a conditional power of 10% for futility. For the purpose of sample size calculation, subjects are assumed to be accrued at a rate of 19.2 per month with a drop-out rate of 10%. The target accrual is a total of approximately 363 subjects randomized in a 2:1 ratio (242 subjects in the quizartinib group and 121 in the salvage chemotherapy group) over 17 months, to reach required number of events in a reasonable timeframe and to compensate for drop-outs. All calculations for sample size were performed using East® 6.3.

Randomization will be stratified by prior therapy and response, and pre-selected salvage chemotherapy:

Prior therapy and response:

- Relapsed in ≤6 months (not post HSCT)

- Refractory
- Relapsed in ≤6 months post allogeneic HSCT

Pre-selected chemotherapy, even for subjects subsequently randomized to quizartinib:

- High intensity chemotherapy (MEC; FLAG-IDA)
- Low intensity chemotherapy (LoDAC)

Primary Efficacy Analysis

Primary efficacy analyses will take place after the required number of events (deaths), 140 events (deaths) at the interim analysis or 280 events (deaths) at the final analysis, has occurred.

The primary efficacy endpoint (OS) analysis will be based on the stratified log-rank test. The stratification factors will be those used for randomization. A non-stratified log-rank test will be used as supportive evidence of efficacy. These analyses will be performed on the intent-to-treat (ITT) analysis data set, consisting of data from all subjects randomized.

Kaplan-Meier methods will be used to estimate OS in each treatment group, both overall and within subsets of subjects defined by the stratification factors. Estimates of median survival will be provided with 95% confidence intervals. Hazard ratio estimates will also be presented.

Overall survival will be censored at the last date when subjects were known to be alive. For primary analysis, OS will not be censored at the time of receipt of subsequent non protocol AML therapy, including transplantation.

Secondary Efficacy Analysis

The secondary efficacy endpoint of EFS will be analyzed using the stratified log-rank test with covariates to control for prior therapy and response to first-line AML therapy and pre-selected salvage chemotherapy in the ITT population. To maintain the overall type 1 error rate at the 0.05 significance level, hypothesis testing in the secondary analysis will be performed only if the null hypothesis in the primary analysis is rejected at the overall two-sided 0.05 significance level.

These analyses will be repeated for the per protocol set (PPS). In addition, the primary efficacy endpoint (OS) and secondary efficacy endpoint (EFS) will be analyzed for pre-defined sub-groups.

Additional Efficacy Analyses

Statistical analyses of exploratory efficacy endpoints include:

- Kaplan-Meier analysis of duration of CRc and CR.
- Cochran-Mantel-Haenszel (CMH) test of CR rate
- CMH test of CRc rate
- CMH test of transplantation rate

Safety Analyses

The safety analysis set (SAF) includes all subjects receiving at least 1 dose of study treatment

(quizartinib or salvage chemotherapy).

Safety evaluation will be based mainly on AEs, clinical laboratory test results, physical examination results, vital signs, ECG results and ECOG performance scores. Descriptive statistics will be used to summarize safety data. All safety data will be summarized by treatment (quizartinib or salvage chemotherapy). The safety data will also be summarized for pre-defined sub-groups.

All summaries of AEs will include only treatment-emergent events unless otherwise stated. Adverse events will be categorized by system organ class and preferred term using the MedDRA dictionary (version 14.1), and will be graded according to NCI CTCAE v4.03.

Additional safety analysis for subjects in post-HSCT quizartinib arm may be performed.

Additional Analyses

AML mutations, pharmacogenomic, pharmacoproteomic, and pharmacoeconomic analyses will be performed.

Interim Analysis

The study design provides for one formal interim analysis when 50% (140) of the final number of events have been observed. At the discretion of the DMC, one of the following actions will occur at this interim analysis:

- Termination of the study for futility

- Termination of the study for efficacy

- Continuing the study as planned

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2.   ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ALL	Acute lymphocytic leukemia
ALT	Alanine transaminase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate transaminase
AUC	Area under the concentration-time curve
AUC_{0-inf}	Area under the concentration-time curve from time 0 to infinity
CFR	Code of Federal Regulations
C_{max}	Maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CP	Conditional power
CR	Complete remission; complete response
CR_c	Composite complete remission (CR+CRi+CRp)
CRF	Case report form
CRi	Complete remission with incomplete hematologic recovery
CRO	Clinical research organization; contract research organization
CRp	Complete remission with incomplete platelet recovery
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Minimum plasma concentration
CV	Coefficient of variation
CYP	Cytochrome P450
DMC	Data monitoring committee
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EMA	European Medicines Agency
FDA	Food and Drug Administration
FLAG-IDA	Fludarabine, cytarabine, and G-CSF with idarubicin
FLT3	FMS-like tyrosine kinase 3
G-CSF	Granulocyte-colony stimulating factor
GCP	Good Clinical Practice
GVHD	Graft versus host disease
HIPAA	Health Insurance Portability and Accountability Act
HSCT	Hematopoietic stem cell transplantation
IC_{50}	Concentration producing 50% inhibition

Abbreviation	Term
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
ITD	Internal tandem duplication
ITT	Intent-to-treat
IV	Intravenous
LFS	Leukemia-free survival
LoDAC	Low dose cytarabine
LVEF	Left ventricular ejection fraction
MDS	Myelodysplastic syndrome
MEC	Mitoxantrone, etoposide, and intermediate-dose cytarabine
MedDRA	Medical Dictionary for Regulatory Activities
msec	Millisecond
MTD	Maximum tolerated dose
MUGA	Multiple gated acquisition
NCI	National Cancer Institute
NR	No evidence of response
NYHA	New York Heart Association
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PGX	Pharmacogenomic(s)
PK	Pharmacokinetic(s)
PPS	Per protocol set
PR	Partial remission; partial response
PT	Prothrombin time
QT	Interval between the start of the Q wave and the end of the T wave
QTc	Corrected QT interval
QTcF	QTc with Fridericia's correction factor
RBC	Red blood cell(s)
RTK	Receptor tyrosine kinase
SAC	Statistical analysis center
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Stable disease; standard deviation

Abbreviation	Term
SRC	Study review committee
TdP	Torsade de pointes
TKI	Tyrosine kinase inhibitor
t_{max}	Time to maximum plasma concentration
ULN	Upper limit of normal
US	United States
WBC	White blood cell(s)

3.   INTRODUCTION

Quizartinib is a novel oral second-generation Class III receptor tyrosine kinase inhibitor with potent activity against FMS-like tyrosine kinase 3 (FLT3) both in vitro and in vivo. It is currently under development for the indication of the treatment of subjects 18 years of age or older with relapsed (including after hematopoietic stem cell transplantation [HSCT]) or refractory FLT3-internal tandem duplication (ITD) positive (+) acute myeloid leukemia (AML), and has been granted Fast Track Status in the United States and an Orphan Drug Indication in the United States and Europe.

FLT3 is expressed in hematopoietic progenitor cells, and signaling through FLT3 promotes these cells' proliferation and differentiation. FLT3 is mutated in approximately 30% of subjects with AML; the mutations include ITD of the juxtamembrane domain of FLT3 and point mutations, usually in the kinase domain. Both types of mutations constitutively activate FLT3 and contribute to leukemic transformation of hematopoietic cells.[1]

There is an unmet medical need for effective treatment for patients with relapsed/refractory AML, and specifically for those with the FLT3-ITD mutation. The FLT3-ITD mutation is associated with a shorter duration of response, a greater cumulative incidence of relapse, and shorter survival after relapse.[2] It has been identified as the worst single prognostic factor in AML for duration of complete remission (CR) and relapse-free survival.[3]

3.1.   Rationale for Development of Quizartinib

Quizartinib selectively inhibits survival pathways that block apoptosis by inhibiting FLT3. Quizartinib inhibits proliferation of FLT3-dependent cell lines, and is effective in human leukemia tumor xenograft models of AML. Data from the Phase 1 and Phase 2 studies have shown a high response rate, even in patients who were refractory to prior chemotherapy.[4,5,8]

3.2.   Nonclinical Studies

Please refer to the current quizartinib Investigator's Brochure for nonclinical data supporting its use in clinical studies.

3.3.   Clinical Studies

A brief summary is given below. Refer to the current quizartinib Investigator's Brochure for additional information on clinical experience with quizartinib.

As of 22 Jan 2016, a total of 1289 subjects received quizartinib in 19 clinical studies including 624 subjects with either AML or solid tumors, 472 healthy volunteers, and 193 subjects with AML, ALL and MDS in 4 investigator sponsored trials.

Quizartinib was studied in 76 AML subjects in a Phase 1 study 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.[8] Plasma taken from subjects and assayed in an in vitro plasma inhibitory assay, showed maximal inhibition of FLT3-ITD signaling at 60 mg dose as early as 2 hours after the first dose. A marked reduction of FLT3-ITD phosphorylation in vivo was also observed at 60 mg and

higher doses. The overall response rate was 53% in FLT3-ITD(+) subjects and 14% in FLT3-ITD(-) subjects.

The response rate observed in Phase 1 was confirmed in the Phase 2, AC220-002 study 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 CRc rate was 57% in FLT3-ITD(+) subjects with a median survival of 25.3 weeks.[4] Cohort 2 showed a CRc rate of 46% in FLT3-ITD(+) subjects with a median survival of 24.0 weeks.[5] Importantly, 35% of Cohort 2 FLT3-ITD(+) subjects were bridged to HSCT. Almost all (94%) subjects proceeding to HSCT had achieved a CRc or partial remission (PR) on quizartinib and their 1 year survival rate was 39%.

The maximum tolerated dose (MTD) determined in the Phase 1 study was 200 mg continuous daily dosing, but in the Phase 2, AC220-002 Study 35% of subjects initially dosed with 200 mg experienced Grade 3 QT prolongation at this dose and therefore the dose was reduced to 135 mg in males and 90 mg in females with the dose differential between sexes due to suspected greater susceptibility of females to QT prolongation. However, exposure-response analysis of the Phase 2 study, 2689-CL-2004, suggests no significant difference in the effect of quizartinib concentrations on QTcF between men and women. A single case of Grade 4 QT prolongation, Torsades de Pointes (TdP), was reported in the AC220-002 Study in a female subject receiving the 90 mg quizartinib dose and concurrently taking a strong CYP3A4 inhibitor. 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 AC220-002 Study (Table 1). QT prolongation was dose dependent and was substantially reduced at the lower doses (Table 2).

Table 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%
PR rate	13%	24%	25%	28%	50%

Table 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)***	**90 mg (N=57)**	**135 mg (N=67)**	**200 mg (N=12)**
Maximum value of QTcF (msec)					

> 480 to ≤ 500 (Grade 2)	5%	14%	21%	13%	33%
> 500 (Grade 3 [asymptomatic])	5%	3%	21%	15%	42%
Maximum change in QTcF from baseline (msec)					
≤ 30	50%	44%	9%	9%	0%
> 30 to ≤ 60	47%	36%	46%	51%	8%
> 60	3%	19%	46%	39%	92%

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

Common adverse events 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.

There are insufficient data to exclude the risk of phototoxicity/photosensitivity reactions due to quizartinib. Excessive exposure to sunlight and other UV light exposure should be avoided. Subjects should be advised to contact the Investigator if they develop a rash or exaggerated sunburn in exposed areas of skin.

Pharmacokinetic data for quizartinib and AC886 from clinical studies in both healthy subjects and AML subjects have been evaluated. Pharmacokinetic profiles were similar across subjects, with quizartinib plasma levels rising rapidly (time to maximum plasma concentration [t_{max}] 1 to 8 hours during the first day of dosing). Quizartinib and AC886 had long effective half-lives of approximately 3 days, resulting in approximately 4-fold accumulation at steady state. Plasma quizartinib concentrations were dose proportional over a tested dose range of 30 mg to 90 mg. Overall, C_{max} and AUC showed moderate to high variability. The primary route of quizartinib elimination was non-renal clearance, and both quizartinib and AC886 were primarily metabolized by CYP3A4. Quizartinib has been shown to be an inhibitor of human efflux transporter P-glycoprotein (P-gp) in-vitro. In addition, quizartinib and its active metabolite AC886 have been shown to be in vitro substrates of P-gp.

A food-effect study involving single dose administration of a 30-mg tablet of quizartinib to healthy volunteers under fasting conditions or with a high-fat meal indicated that AUC was increased by approximately 8% while the 90% CI of the C_{max} ratio of fed to fasting condition was contained within the 80 to 125% 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, Tmax, by approximately 2 hours.

A drug-drug interaction (DDI) study was conducted with the proton pump inhibitor lansoprazole. Healthy subjects were randomized to receive quizartinib 30-mg tablet alone or lansoprazole 60-mg administered once daily for 5 days with a single dose of a 30-mg tablet of quizartinib administered on day 5. A weak PK drug-drug interaction was observed between quizartinib and lansoprazole; Cmax and AUC decreased 14% and 5%, respectively, for quizartinib. 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.

4.   STUDY OBJECTIVES

4.1.   Primary Objective

The primary objective of the study is to determine whether quizartinib monotherapy prolongs overall survival (OS) compared to salvage chemotherapy in subjects with FLT3-ITD(+) AML who are refractory to or have relapsed within 6 months, after first-line AML therapy.

4.2.   Secondary Objectives

The secondary objective of the study is to determine event-free survival (EFS) following treatment with quizartinib versus salvage chemotherapy.

4.3.   Exploratory Objectives

Exploratory objectives are:

- to compare the composite complete remission [CRc = complete remission (CR) + complete remission with incomplete platelet recovery (CRp) + complete remission with incomplete hematologic recovery (CRi)] rate (Response definitions provided in Section 7.2)

- to compare the complete remission (CR) rate

- to compare the duration of CRc

- to compare the duration of CR

- to determine leukemia-free survival (LFS)

- to compare the transplantation rate

- to determine the QTc prolonging effects of quizartinib in relation to plasma drug concentrations

- to determine the pharmacokinetics (PK) of quizartinib and its active metabolite, AC886

- to determine the exposure-response relationship

- to determine resource utilization in this study population

- to identify AML-associated mutations and their frequencies

- pharmacogenomic and pharmacoproteomic determinations

5. STUDY DESIGN

5.1. Overall Study Design and Plan

This is a Phase 3, randomized, open-label, 2-arm study to compare the effect of quizartinib monotherapy and salvage chemotherapy on OS in subjects with FLT3-ITD(+) AML that is refractory or relapsed within 6 months, after first-line therapy with or without consolidating HSCT. The control treatment is a limited choice of one of three standard chemotherapy regimens (low dose cytarabine [LoDAC]; mitoxantrone, etoposide, and intermediate-dose cytarabine [MEC]; or fludarabine, cytarabine, and granulocyte-colony stimulating factor (G-CSF) with idarubicin [FLAG-IDA]) which are widely used to treat patients with AML. Prior to randomization, the Investigator will pre-select one of the three salvage chemotherapy regimens for each subject; doses and the duration of study treatments are outlined in Section 5.6.4.2.

The study will utilize a group sequential design with 1 interim look at 0.5 information fraction (ie, 50% of planned number of events [deaths]). The target sample size will be approximately 363 subjects, randomized in a 2:1 ratio to receive quizartinib monotherapy (242 subjects) or salvage chemotherapy (121 subjects). One formal interim analysis will be performed by an independent statistical analysis center (SAC) and evaluated by an independent data monitoring committee (DMC), according to statistical procedures defined a priori. Based on the results of the interim analysis, the DMC may recommend that the study be terminated early for futility or for efficacy, or continue as planned. The tasks performed by the SAC and DMC are described in the DMC charter and Interim Analysis Plan.

If the study is positive at the pre-specified interim or final analysis, the sponsor may allow subjects who did not receive quizartinib to cross-over to the quizartinib monotherapy arm after database lock if the safety parameters in the eligibility criteria are met (see Section 5.4). The study will be unblinded after database lock.

5.1.1. Screening

During the 14 day screening period, subjects will undergo medical history evaluation, physical examination, vital sign determination, Eastern Cooperative Oncology Group (ECOG) performance status assessment, chest X-ray, concomitant medication assessment, blood and urine sampling for laboratory tests, ECG monitoring, and bone marrow aspiration or biopsy to confirm FLT3 ITD status, multiple gated acquisition (MUGA) scans or echocardiography (ECHO).

5.1.2. Treatment

A flow chart of study activities is presented in Figure 1.

For subjects randomized to quizartinib the starting dose will be 30 mg/day unless the subject is receiving concurrent therapy with a strong CYP3A4 inhibitor, in which case the starting dose will be 20 mg/day. The dose will be taken in the morning with or without food over continuous 28-day cycles. If the subject omits taking quizartinib in the morning, it may be taken later in the day (until midnight), otherwise the dose should be considered missed. If the subject vomits after

taking quizartinib, no replacement dose should be given. Detailed information on quizartinib dosing is provided in Section 5.6.4.1.

The dose of quizartinib will be increased at Day 16 or Cycle 2 Day 1 according to the criteria specified in Section 5.6.4.3. Following dose escalation, triplicate ECG determinations should be performed at least once weekly for 2 weeks to monitor QTcF prolongation.

If necessary, the dose of quizartinib may be reduced according to the criteria described in Section 5.6.4.4.

See also Section 8.5 for details of QTcF management when prolongation is observed.

In subjects receiving quizartinib or LoDAC, treatment should continue until there is no longer clinical benefit from therapy, or until unacceptable toxicity occurs. For subjects receiving LoDAC the initiation of cycles may be delayed for up to 14 days to allow for recovery from toxicity.

Subjects that receive either quizartinib or LoDAC will be assessed for response on Day 1 of Cycle 2 and Day 1 of Cycle 3 as well as on Day 1 of each subsequent cycle unless the subject has already achieved CR, CRp, or CRi. In that event, bone marrow testing will be repeated after every 3 subsequent cycles, unless there is evidence of relapse.

Subjects receiving MEC or FLAG-IDA will receive 1 cycle of therapy and be assessed for response at Day 29 (± 14 days). Salvage chemotherapy should be given as 28 day cycles, although cycles may be delayed for recovery from toxicity or blood count recovery for up to 14 days. Subjects achieving complete remission (CR), complete remission with incomplete hematologic recovery (CRi), or complete remission with incomplete platelet recovery (CRp) by Investigator assessment, may receive a second cycle of the same therapy at the Investigator's discretion. Treatment should be discontinued if there is no evidence of response (NR) or progressive disease (PD). Subjects classified as being in NR must have at least one evaluable bone marrow aspirate or biopsy and not meet the criteria for PR or better.

For subjects who do not have evaluable bone marrow aspirate or biopsy, but have presence of leukemic blasts in the peripheral blood, the response is considered as NR. For subjects who demonstrate some level of clinical benefit but do not achieve a remission, the decision on additional treatment is at the Investigator's discretion.

Figure 1.   Flow Chart of Study Activities
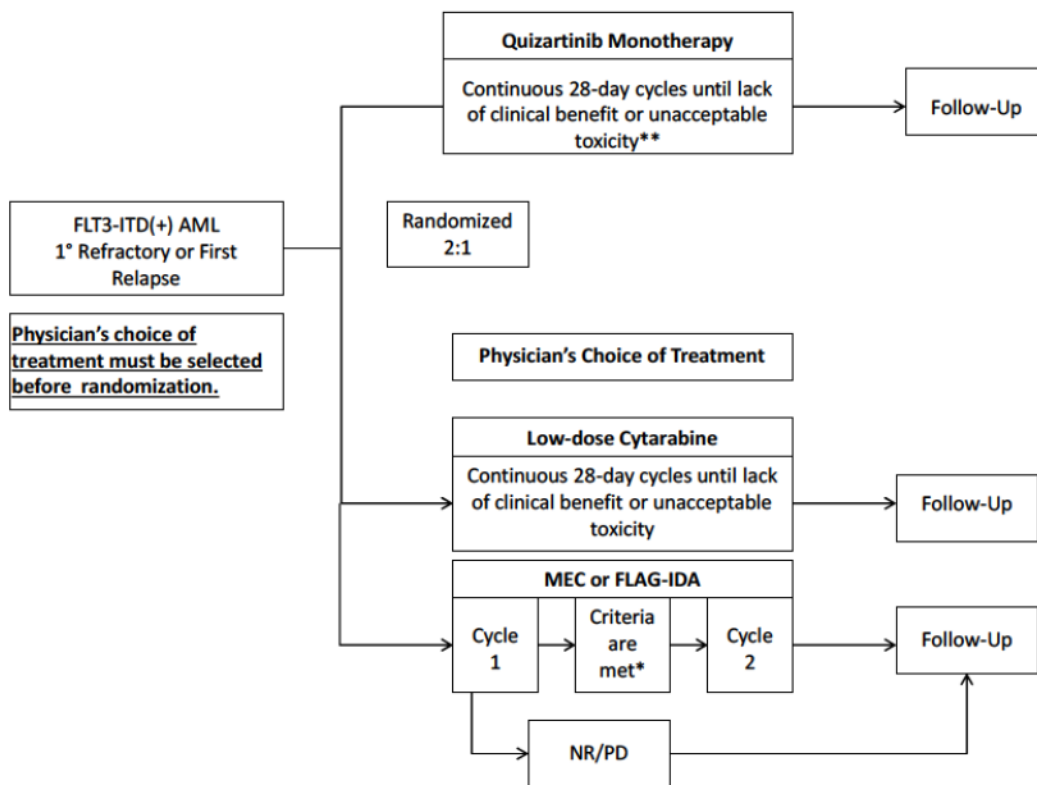
* Subjects receiving MEC or FLAG-IDA will receive 1 cycle of therapy and may receive a second cycle of the same therapy at the Investigator's discretion. Treatment should be discontinued if there is no evidence of response (NR) or progressive disease (PD). For subjects who achieve a reduction in blast count but no CR, CRp or CRi, the investigator should determine whether or not a second cycle is likely to be beneficial, based on the level of response to the first cycle, toxicity and performance status of the subject..

** Subjects in the quizartinib arm who proceed to HSCT may resume quizartinib administration between 30 and 100 days after transplantation.

5.1.3.   Follow-up

After study treatment is discontinued, subjects will be followed for 30 days for safety. Subjects will then enter long term follow-up for collection of information on subsequent AML treatment, remission status, and survival, including the cause and date of death.

5.2.   Rationale for Study Design and Dosing

5.2.1.   Rationale for Study Design

AC220-007 is a randomized Phase 3 study to determine the clinical benefit of single agent quizartinib for the treatment of relapsed or refractory FLT3-ITD positive AML. There are currently no approved therapies that target the FLT3-ITD mutation in AML and previous Phase 1 and 2 studies with quizartinib have shown a high response rate even in patients who were refractory to prior chemotherapy.

Enrollment in the AC220-007 study is restricted to FLT3-ITD(+) AML subjects who are either refractory to induction chemotherapy or have relapsed within 6 months after achieving CR including after a prior allogeneic HSCT, as these subject populations have few treatment options. In the Phase 2, AC220-002 Study, the CRc rate, transplantation rate and overall survival of subjects receiving quizartinib as a second salvage treatment exceeded that reported in a recent study of FLT3-ITD(+) subjects receiving first salvage chemotherapy.[6] Additionally, the response rate, transplantation rate and survival of subjects receiving quizartinib in the AC220-002 Study also exceeded that reported in a large series of AML subjects receiving second salvage.[7]

The planned enrollment of 363 subjects was based on the requirement for 280 events to provide 90% power assuming a hazard ratio of 0.65. This estimated hazard ratio is based on data from the Phase 2, AC220-002 study and historical data. In the AC220-002 study, FLT3-ITD(+) subjects in Cohort 1 who were 60 years or older, relapsed or refractory after 1 line of AML therapy had a median survival of 25 weeks.[4] Published data on survival of a series of relapsed FLT3-ITD(+) patients show a median survival of 13 weeks.[2] Those subjects in the AC220-002 study Cohort 1 who relapsed within 6 months had a median survival of 25 weeks compared to data from a recent randomized study which showed a median survival of 14 weeks for FLT3-ITD(+) subjects receiving salvage therapy after a CR of less than 6 months.[6] In Cohort 2, subjects were 18 years or older relapsed or refractory after 1 line of salvage therapy or relapsed after HSCT, had a median survival of 24 weeks.[5] This compares to a median survival of 6 weeks in a large series of AML patients including FLT3-ITD positive and negative patients who were relapsed or refractory to salvage therapy, and receiving second salvage.[7]

5.2.2.   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(+), however, for the Phase 3 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. Analysis of "ITD(-)" subjects from the AC220-002 Study 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.

5.2.3.   Selection of 30 mg Daily for the Quizartinib Starting Dose

The dose of quizartinib selected for the Phase 3 study is based on data from the Phase 1 (CP0001) Study, and Phase 2 (AC220-002 and 2689-CL-2004) Studies in approximately 480 subjects with relapsed or refractory AML.

In the Phase 1 study, 76 subjects were enrolled. A total of 51 subjects received quizartinib on an intermittent schedule (at daily doses of 12 mg to 450 mg) and 25 subjects received quizartinib on a continuous schedule (200 mg to 300 mg daily), of which 17 subjects total were determined to be FLT3-ITD(+). Plasma was collected from subjects at specific time points following initiation of quizartinib administration and tested for the ability of quizartinib to inhibit FLT3-ITD phosphorylation in an in vitro plasma inhibitory assay. Complete and sustained inhibition of phosphorylation was observed in the 60 mg cohort as early as 2 hours after the first dose, and

remained at day 28, whereas at 18 mg only partial inhibition was observed at 2 hours and the inhibition was not as durable.[8] Compensatory mechanisms that will potentially overcome FLT3 inhibition can reduce the effect of FLT3 inhibitors on leukemic blasts. These mechanisms include over-expression of FLT ligand and physical contact with bone marrow stromal cells, which both increase the concentration of inhibitor required to block proliferation or induce apoptosis by a factor of 3 to 5 fold.[9] Therefore, selection of a dose that has complete and long-lasting inhibition of FLT3-ITD signaling is critical to maintain blockade of FLT3 signaling and for sustained clinical efficacy.

In the Phase 2 AC220-002 Study, the first 17 subjects enrolled received 200 mg/day (the MTD from the Phase 1 study) of quizartinib as a starting dose. Due to QTcF prolongation, the dose was reduced and the remaining 316 subjects received either 135 mg/day (primarily males) or 90 mg/day (all females). In the Phase 2b 2689-CL-2004 Study, both males and females were randomized to either 30 mg/day or 60 mg/day.

When comparing the efficacy in a similar patient population across the 5 daily starting doses studied in the Phase 2 studies [AC220-002 doses of: 200 mg/day, 135 mg/day, and 90 mg/day; and in 2689-CL-2004 doses of: 60 mg/day, and 30 mg/day] there is no overall difference in the CRc rates (Section 3.3; Table 1). The CRc rates at each dose were: 42% at 200 mg/day; 45% at 135 mg/day; 47% at 90 mg/day; 47% at 60 mg/day; and 47% at 30 mg/day. However, the PR rates (13% vs. 24%, respectively) were higher in the 60 mg/day group compared to 30 mg group. Additionally, the percentage of dose modifications was similar for dose reductions (32% and 31% for 30 mg and 60 mg dose groups, respectively) but there was a difference in the dose increases due to lack of response. In the 38 subjects treated at 30 mg/day as the starting dose, 24 (63%) underwent dose escalation to 60 mg/day compared to 7 (19%) who were dose escalated from 60 mg to 90 mg.

Overall there were no major differences in adverse events experienced by subjects in the 30 mg/day and 60 mg/day dose groups. The QTcF prolongation following administration of quizartinib was clearly dose dependent in the AC220-002 Study and this was confirmed in the Phase 2b 2689-CL-2004 Study (Section 3.3; Table 2). The Grade 2 or greater QTcF prolongation was 11% in subjects (4/38) at 30 mg/day and 17% in subjects (6/36) at 60 mg/day in the Phase 2b 2689-CL-2004 Study. In addition, Grade 3 QTcF prolongation was seen with a much lower frequency in the Phase 2b 2689-CL-2004 Study at both doses (5% and 3% at 30 mg and 60 mg respectively) compared to that reported at the higher doses in Study AC220-002, which showed 42% Grade 3 QTcF prolongation at the starting dose of 200 mg/day, 15% at 135 mg/day, and 21% (which included 1 case of Grade 4 QTcF prolongation that resolved after quizartinib discontinuation) at 90 mg/day. Of importance, there were no Grade 4 QT prolongation events in the Phase 2b study.

The quizartinib starting dose for this study will be 30 mg/day with dose escalation to 60 mg after 15 or 28 days according to the criteria specified in Section 5.6.4.3. This dose was selected based on the need to maintain a high level of efficacy in a very aggressive disease with a poor overall prognosis, while at the same time minimizing toxicity.

5.2.4. Quizartinib Dose Reduction with Strong CYP3A4 Inhibitors

Data from Study AC220-015, which examined the effect of strong and moderate CYP3A4 inhibitors on quizartinib PK in human volunteers, show that concomitant ketoconazole, a strong

CYP3A4 inhibitor, increased quizartinib $AUC_{0\text{-}inf}$ and steady state C_{max} (after repeat daily dosing) approximately 2-fold, and concomitant fluconazole, a moderate CYP3A4 inhibitor, increased quizartinib $AUC_{0\text{-}inf}$ and steady state C_{max} approximately 1.2-fold. Subjects receiving concomitant medication with a strong CYP3A4 inhibitor on Day 1, and who are randomized to quizartinib, will take 20 mg/day. Subjects who begin treatment with a strong CYP3A4 inhibitor while receiving quizartinib will be required to be reduced from either 60 mg/day to 30 mg/day or from 30 mg/day to 20 mg/day. If the subject discontinues the strong CYP3A4 inhibitor, the dose of quizartinib can be resumed at the prior dose. No dose reduction of quizartinib is required when subjects are co-administered a moderate or weak CYP3A4 inhibitor. See Appendix 1: List of Potential QT Prolonging Drugs, CYP3A4 Inhibitors/Inducers, and P-glycoprotein Inhibitors/Inducers.

5.2.5.   Treatment with Quizartinib Following HSCT

Allogeneic transplant has become an accepted standard of care for consolidating newly diagnosed FLT3-ITD AML subjects in first remission.[10,11,12] Additionally, treatment consensus guidelines recommend HSCT for subjects with relapsed AML regardless of FLT3-ITD status whenever feasible. Based on data from the Phase 2 studies, approximately 35% of subjects will likely be bridged to HSCT in the Phase 3 AC220-007 Study.

The post-HSCT relapse rate for FLT3-ITD positive AML subjects is higher than that observed for other AML sub-groups undergoing consolidation HSCT, and the leukemia cells at relapse are typically highly addicted to FLT3-ITD signaling.[13]

The use of a TKI to induce remission and then as maintenance post-HSCT has been established in BCR-ABL acute lymphocytic leukemia (Ph+-ALL). In adults with Ph+ ALL, HSCT is an established treatment standard of care,[14] and BCR-ABL TKIs are not only used to bridge patients to transplant, they are routinely used post-HSCT to maintain remission and prolong survival.[15,16] In terms of AML, a FLT3 inhibitor (sorafenib) currently approved for other oncology indications has been reported to have activity in the post-HSCT setting.[17] Given current standard practice with BCR-ABL TKIs in Ph+ ALL, for subjects randomized to the quizartinib treatment group, quizartinib will be offered to those subjects undergoing HSCT with the aim of reducing the high risk of relapse post-HSCT and to evaluate whether administration of quizartinib before HSCT and as maintenance following HSCT, is of clinical benefit.

A phase 1 study (A Phase 1 Study of AC220 [ASP2689] as Maintenance Therapy in Subjects with Acute Myeloid Leukemia who Have Been Treated with an Allogeneic Hematopoietic Stem Cell Transplant: 2689-CL-0011) enrolled 13 subjects who were in remission following an allogeneic HSCT. 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. Preliminary data have shown that both doses are well tolerated with 5/7 (71%) subjects in the 40 mg cohort and 6/6 (100%) subjects in the 60 mg cohort remaining on quizartinib without disease relapse. There were 8 subjects who discontinued treatment: (one due to progressive disease, two per the Investigator's discretion, four due to Serious Adverse Events (SAEs), and one for reasons that were not specified), with 10 of 13 subjects receiving quizartinib for more than 1 year.

5.3.   Study Duration

Time from enrollment of first subject to the 280th event (death) should be approximately 36 months.

5.4.   Selection of Study Population

5.4.1.   Inclusion Criteria

To be able to participate in this study, candidates must meet the following criteria at screening or other specified time point:

1. Provision of written informed consent approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) with privacy language in accordance with national regulations (eg, HIPAA authorization for US sites) prior to any study-related procedures, including withdrawal of prohibited medications if applicable.

2. Age ≥18 years or the minimum legal adult age (whichever is greater) at the time of informed consent.

3. Morphologically documented primary AML or AML secondary to myelodysplastic syndrome (MDS), as defined by World Health Organization criteria, as determined by pathology review at the study site.

4. In first relapse (with duration of remission of 6 months or less) or refractory after prior therapy, with or without HSCT. Induction therapy must have included at least 1 cycle of an anthracycline/mitoxantrone-containing induction block at a standard dose.

   - Refractory is defined as:

     - After 1 cycle, a reduction in bone marrow blasts of less than 50% and failure to achieve a CR, CRp, or CRi.

     - After 2 cycles, lack of achievement of CR, CRp, or CRi.

   - First relapse (with duration of remission of 6 months or less) is defined as:

     - Achievement of CR, CRi, or CRp, as defined by 2003 International Working Group criteria (Section 7.2) after initial AML therapy with or without consolidation or maintenance, and with or without HSCT.

     - Duration of CR, CRi or CRp is measured from the date of the bone marrow assessment which confirmed response or the date of allogeneic transplantation, to the date of the bone marrow assessment that identified relapse or the appearance of peripheral blasts.

5. Presence of the FLT3-ITD activating mutation in bone marrow or peripheral blood (allelic ratio as determined by a central laboratory with a cutoff of ≥3% FLT3-ITD/total FLT3). If a specimen has been sent for FLT3-ITD testing at the central laboratory but the subject requires treatment for AML before the central FLT3-ITD test result is available, a local test result may be acceptable for randomization after consultation with the Medical Monitor.

6. Eligibility for pre-selected salvage chemotherapy, according to the Investigator's assessment.

7. ECOG performance score 0-2.

8. Discontinuation of prior AML treatment before the start of study treatment (except hydroxyurea or other treatment to control leukocytosis) for at least 2 weeks for cytotoxic agents, or for at least 5 half-lives for non-cytotoxic agents.

9. Serum creatinine ≤1.5×upper limit of normal (ULN), or glomerular filtration rate >25 mL/min, as calculated with the Cockcroft-Gault formula.

10. Serum potassium, magnesium, and calcium (serum calcium corrected for hypoalbuminemia) within institutional normal limits. Subjects with electrolytes outside the normal range will be eligible if these values are corrected upon retesting following any necessary supplementation.

11. Total serum bilirubin ≤1.5×ULN.

12. Serum aspartate transaminase (AST) and/or alanine transaminase (ALT) ≤2.5×ULN.

5.4.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following criteria are met at screening or other specified time point:

1. Acute promyelocytic leukemia (AML subtype M3)

2. AML secondary to prior chemotherapy for other neoplasms, except AML secondary to prior MDS

3. History of another malignancy, unless the candidate has been disease-free for at least 5 years

   - Candidates with treated non-melanoma skin cancer, carcinoma in situ, or cervical intraepithelial neoplasia are eligible regardless of the time spent disease-free, if they have completed definitive treatment

   - Candidates with organ-confined prostate cancer, with no evidence of recurrent or progressive disease, are eligible if hormonal therapy has been begun, or if the tumor has been surgically removed or treated with definitive radiotherapy

4. Persistent, clinically significant > Grade 1 non-hematologic toxicity from prior AML therapy

5. Clinically significant GVHD or GVHD requiring initiation of treatment or treatment escalation within 21 days, and/or > Grade 1 persistent or clinically significant non-hematologic toxicity related to HSCT

6. History of or current, central nervous system involvement with AML

7. Clinically significant coagulation abnormality, such as disseminated intravascular coagulation

8. Prior treatment with quizartinib or participated in a prior quizartinib study

9. Prior treatment with a FLT3 targeted therapy including sorafenib or investigational FLT3 inhibitors (not including the multi-kinase inhibitor, midostaurin)

10. Major surgery within 4 weeks prior to screening

11. Radiation therapy within 4 weeks prior to screening

12. Uncontrolled or significant cardiovascular disease, including:

   - QTcF interval >450 msec (average of triplicate determinations)

   - Subject has bradycardia of less than 50 BPM (as determined by central reading) unless the subject has a pacemaker

   - Diagnosed or suspected long QT syndrome, or known family history of long QT syndrome

   - History of clinically relevant ventricular arrhythmias, such as ventricular tachycardia, ventricular fibrillation, or torsade de pointes

   - History of second or third degree heart block. Candidates with a history of heart block may be eligible if they currently have pacemakers, and have no history of fainting or clinically relevant arrhythmia with pacemakers.

   - Myocardial infarction within 6 months prior to screening

   - Uncontrolled angina pectoris within 6 months prior to screening

   - New York Heart Association (NYHA) Class 3 or 4 congestive heart failure

   - Left ventricular ejection fraction (LVEF) ≤45% or institutional lower limit of normal

   - Uncontrolled hypertension

   - Complete left or right bundle branch block

13. Active infection not well controlled by antibacterial, antifungal, and/or antiviral therapy

14. Known infection with human immunodeficiency virus, or active hepatitis B or C, or other active clinically relevant liver disease

15. Unwillingness to receive infusion of blood products according to the protocol

16. In a man whose sexual partner is a woman of childbearing potential, unwillingness or inability of the man or woman to use a highly effective contraceptive method for the entire study treatment period and for at least 3 months after study treatment completion

   - Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and 105 days after the final study drug administration.

17. In a heterosexually active woman of childbearing potential, unwillingness or inability to use a highly effective contraceptive method for the entire study treatment period and for at least 3 months after study treatment completion. Additionally, for women

randomized to chemotherapy, unwillingness to adhere to the restrictions respective locally established guidelines and local approved label (prescribing information, Summary of Product Characteristics, or US product insert) from the manufacturer and the Patient Information Leaflet (package insert) as instructed by the Investigator.

- Women are not regarded as of childbearing potential if they are post-menopausal (at least 2 years without menses) or are surgically sterile (at least 1 month before study).

- Highly effective contraception methods include: hormonal methods associated with inhibition of ovulation, intra-uterine device; surgical sterilization (including partner's vasectomy) or sexual abstinence if this is the preferred and usual lifestyle of the subject.

- Female subjects must not donate or retrieve, for their own use, ova from the time of Screening and throughout the study treatment period, and for 12 weeks after the final study drug administration.

18. Pregnancy

19. Female subjects must agree not to breastfeed from the time of Screening and throughout the study period, and for 25 days after the final study drug administration.

20. Medical condition, serious intercurrent illness, or other circumstance that, in the Investigator's judgment, could jeopardize the candidate's safety as a study subject, or that could interfere with study objectives.

21. For subjects in the UK only: Refusal of permission to allow the subject's General Practitioner to be notified of their participation in the study.

5.4.3.   Inclusion of Women, Minorities, and Other Underrepresented Populations

This study is open to all subpopulations of subjects who fulfill eligibility criteria.

5.4.4.   Eligibility to Cross-Over to Quizartinib from Salvage Chemotherapy

5.4.4.1.   Inclusion Criteria for Cross-Over

To be able to cross-over to quizartinib therapy from salvage chemotherapy, candidates must meet the following criteria at screening or other specified time point:

1. Provision of written informed consent approved by the IRB or IEC with privacy language in accordance with national regulations (eg, HIPAA authorization for US sites) prior to any study-related procedures, including withdrawal of prohibited medications if applicable.

2. ECOG performance score 0-2.

3. Serum creatinine $\leq 1.5 \times$ULN, or glomerular filtration rate >25 mL/min, as calculated with the Cockcroft-Gault formula.

4. Serum potassium, magnesium, and calcium (serum calcium corrected for hypoalbuminemia) within institutional normal limits. Subjects with electrolytes outside

the normal range will be eligible if these values are corrected upon retesting following any necessary supplementation.

5. Total serum bilirubin ≤1.5×ULN.

6. Serum AST and/or ALT ≤ 2.5×ULN.

5.4.4.2. Exclusion Criteria for Cross-Over

Candidates will be excluded from cross-over to quizartinib if any of the following criteria are met at Screening or other specified time point:

1. QTcF interval >450 msec (average of triplicate determinations.)

2. Subject has bradycardia of less than 50 BPM (as determined by central reading).

3. Uncontrolled hypertension.

4. Active infection not well controlled by antibacterial, antifungal, and/or antiviral therapy.

5. In a man whose sexual partner is a woman of childbearing potential, unwillingness or inability of the man or woman to continue to use a highly effective contraceptive method for the entire study treatment period and for at least 3 months after study treatment completion:

   - Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and 105 days after the final study drug administration.

6. In a heterosexually active woman of childbearing potential, unwillingness or inability to continue to use a highly effective contraceptive method for the entire study treatment period and for at least 3 months after study treatment completion.

   - Women are not regarded as of childbearing potential if they are post-menopausal (at least 2 years without menses) or are surgically sterile (at least 1 month before study).

   - Highly effective contraception methods include: hormonal methods associated with inhibition of ovulation, intra-uterine device; surgical sterilization (including partner's vasectomy); or sexual abstinence if this is the preferred and usual lifestyle of the subject.

   - Female subjects must not donate or retrieve, for their own use, ova from the time of screening and throughout the study treatment period, and for 12 weeks after study treatment completion.

7. Pregnancy

8. Female subjects must agree not to breastfeed from the time of Screening and throughout the study period, and for 25 days after the final study drug administration.

9. For subjects in the UK only: Refusal of permission to allow the subject's General Practitioner to be notified of his or her participation in the study.

5.4.5. Subject Withdrawal Criteria

Subjects are free to withdraw consent and discontinue participation in the study at any time and without prejudice to future treatment. A subject's participation in the study may be discontinued

at any time at the Investigator's discretion. Justifiable reasons for a subject to be withdrawn from the study include:

- Noncompliance with study procedures or study site rules, including failure to take study medication or to appear at 1 or more study visits

- Use of any prohibited concomitant medication, supplement, food, or beverage without prior approval by the Investigator and Sponsor

- Erroneous inclusion of the subject in the study

- Major protocol deviation presenting an unnecessary risk to the subject's health

- Lost to follow-up

Study treatments must be withdrawn for any of the following reasons:

- Intolerable AE related to study treatment, including Grade 4 QTcF prolongation

- Resting LVEF <45%

- Pregnancy

- Termination of the study by the Sponsor

- Withdrawal of informed consent for any reason

- Any clinical AE or abnormal laboratory test result indicating, in the Investigator's opinion, that continued study drug dosing is not in the subject's best interest

The reason for subject withdrawal should be recorded on the appropriate case report form (CRF).

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

- Participation in the 30-Day Follow-up Visit per protocol, either in clinic or by telephone;

- 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);

- Study 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 CRF.

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

5.5.   Study or Site Termination

If the Sponsor, the Investigator, the clinical monitor, United States (US) Food and Drug Administration (FDA) or other Competent Authority officials discover conditions during the study indicating that the site's participation should be terminated, this action may be taken after appropriate consultation between the Sponsor and the Investigator. Conditions that may warrant termination of the study include, but are not limited to:

- Discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study

- Sponsor's decision to suspend or discontinue testing, evaluation, or development of the study drug

- Investigator's failure to comply with pertinent US FDA or regional Health Authority regulations and ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) guidelines

- Insufficient compliance with protocol requirements

5.6.   Study Treatment

5.6.1.   Identity of Investigational Product

The investigational medicinal product is supplied to the pharmacy as quizartinib 30 mg yellow tablets (26.5 mg free base) or 20 mg white tablets (17.7 mg free base) of AC010220•2HCl. All packages are shipped at conditions depicted on the product label.

5.6.1.1.   Packaging and Storage

Quizartinib drug will be provided to the site in numbered bottles. Subjects randomized to salvage chemotherapy will receive commercially available chemotherapy.

Quizartinib tablets must be stored appropriately in a locked cabinet/room with limited and controlled access under the recommended storage conditions (store up to 25ºC [77ºF] and protected from freezing). The storage condition of quizartinib drug bottles must be logged daily. If the storage room/cabinet does not have an automated continuous temperature recording system to record the daily temperature data, daily temperature must be monitored and recorded on a temperature log.

Detailed instructions for the handling of quizartinib can be found in the Pharmacy Manual.

5.6.1.2.   Study Drug Accountability

The investigational pharmacy will maintain a record of study drug inventory.

The investigator or designee will maintain subject ID, bottle number, lot number, date dispensed, number of bottles and tablets dispensed and returned on a subject study drug dispensing and accountability log.

5.6.2. Method of Assigning Subjects to Treatment Groups

Upon providing written informed consent and initiation of screening procedures, a unique number will be assigned to each subject. Subjects will maintain this number throughout the study.

Subjects will be randomized into the two treatment groups in a 2:1 ratio (242 quizartinib and 121 salvage chemotherapy) and the randomization will be stratified by prior therapy and response, and pre-selected salvage chemotherapy:

Prior therapy and response:

- Relapsed in ≤ 6 months (not post HSCT)
- Refractory
- Relapsed in ≤ 6 months post allogeneic HSCT

Pre-selected chemotherapy, even for subjects subsequently randomized to quizartinib:

- High intensity chemotherapy (MEC; FLAG-IDA)
- Low intensity chemotherapy (LoDAC)

5.6.3. Selection of Doses in the Study

The full rationale is given in Section 5.2.3.

5.6.4. Selection and Timing of Doses for Each Subject

5.6.4.1. Quizartinib

For subjects randomized to quizartinib the starting dose will be 30 mg/day unless the subject is receiving concurrent therapy with a strong CYP3A4 inhibitor, in which case the starting dose will be 20 mg/day. The dose of quizartinib will be taken in the morning over continuous 28-day cycles. Quizartinib should be taken in the morning. If the subject omits taking quizartinib in the morning, it may be taken later in the day (up to midnight) otherwise the dose is considered missed. If the subject vomits after taking quizartinib, no replacement dose should be given. Criteria for dose escalation or dose reduction are provided in Section 5.6.4.3 and Section 5.6.4.4 respectively.

Quizartinib can be crushed and dissolved in water. The resulting solution can be drawn up in a disposable syringe and administered via polyvinyl chloride or silicone nasogastric tubes. Details can be found in the Pharmacy Manual.

5.6.4.2. Salvage Chemotherapy

The Investigator will pre-select the specific salvage chemotherapy regimen before randomization of each subject. All salvage chemotherapy will be administered during 28-day cycles. The start of Cycle 2 (MEC; FLAG-IDA, or LoDAC) and subsequent cycles (LoDAC) may be delayed for up to 14 days to allow for recovery from toxicity. Dose reductions are allowed for toxicity and must be documented in the source record.

Low Dose Cytarabine (LoDAC)

Cytarabine (20 mg) will be administered twice daily by subcutaneous injection for 10 days (Days 1 through 10) over continuous 28-day cycles. A delay of up to 14 days between cycles is allowed for recovery from toxicity.

MEC Chemotherapy

- Mitoxantrone (8 mg/m^2/day) will be administered by 5 minute intravenous (IV) injection for 5 days (Days 1 through 5).

- Etoposide (100 mg/m^2/day) will be administered by 1 hour IV infusion immediately after mitoxantrone for 5 days (Days 1 through 5).

- Cytarabine (1000 mg/m^2/day) will be administered by 1 hour IV infusion immediately after etoposide for 5 days (Days 1 through 5).

FLAG-IDA Chemotherapy

- G-CSF (300 µg/m^2/day) will be administered by 2 hour IV infusion for 5 days (Days 1 through 5) or alternatively, G-CSF (5 µg/kg/day) may be administered SC for 5 days (Days 1 through 5). Additional G-CSF is recommended 7 days after the completion of chemotherapy, until ANC is >$0.5×10^9$/L.

- Fludarabine (30 mg/m^2/day) will be administered by 30 minute IV infusion for 5 days (Days 2 through 6).

- Cytarabine (2000 mg/m^2/day) will be administered by 4 hour IV infusion, beginning 4 hours after the fludarabine infusion, for 5 days (Days 2 through 6).

- Idarubicin (10 mg/m^2/day) will be administered over 5 to 10 minutes in a fast-running saline drip for 3 days (Days 2 through 4).

5.6.4.3. Quizartinib Dose Escalation Rules and Definitions

CYCLE 1 DAY 16

For subjects not taking a strong CYP3A4 inhibitor the dose of quizartinib will be increased to 60 mg/day starting on Day 16 if the subject's average QTcF (QT interval corrected with Fridericia's formula), based on triplicate reading, is ≤ 450 msec on and before Day 15.

For subjects taking a strong CYP3A4 inhibitor, the dose of quizartinib will be increased to 30 mg/day providing they meet the above QTcF requirements.

CYCLE 2 DAY 1

Subjects who fail to achieve a CR, CRp or CRi as defined in Section 7.2 after at least one 28-day cycle of therapy, and may undergo dose escalation providing the following criteria are met:

- The subject has not had a Grade 3 or higher, non-hematologic, and related adverse event.

- No increase in QTcF more than 60 msec above baseline.

- The subject must not have aplastic bone marrow at the time of the proposed dose escalation.

In addition, subjects who achieved a response (CR, CRi, CRp, or PR) at any time and who subsequently relapsed may undergo dose escalation provided they meet the same criteria as above.

For subjects not taking a strong CYP3A4 inhibitor the dose of quizartinib will be increased to 60 mg/day.

For subjects taking a strong CYP3A4 inhibitor, the dose of quizartinib will be increased to 30 mg/day providing they meet the above requirements.

Following dose escalation, triplicate ECG determinations should be performed at least once weekly for 2 weeks to monitor QTcF prolongation.

5.6.4.4. Quizartinib Dose Reduction Rules and Definitions

The dose of quizartinib will be reduced stepwise from 60 mg/day to 30 mg/day or from 30 mg/day to 20 mg/day, based on the following criteria:

QTcF (QT interval corrected with Fridericia's formula) Prolongation

- Grade 2 (QTcF average of triplicate readings > 480 msec)
  - The dose will be reduced without interruption.
  - If 20 mg/day is the current dose, dosing will be interrupted for up to 14 days. If QTcF returns to within 30 msec of baseline or ≤ 450 msec within 14 days, treatment may be resumed at 20 mg/day.

- Grade 3 (QTcF average of triplicate readings > 500 msec)
  - Dosing will be interrupted for up to 14 days. If QTcF returns to within 30 msec of baseline or ≤450 msec within 14 days, treatment may be resumed at a reduced dose.
  - If 20 mg/day is the current dose, dosing will be interrupted for up to 14 days. If QTcF returns to within 30 msec of baseline or ≤ 450 msec within 14 days, treatment may be resumed at 20 mg/day. If Grade 3 event returns, treatment will be discontinued.

- Grade 4 (QTcF >500 msec or >60 msec change from baseline, and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)
  - Treatment will be discontinued.

See Section 8.5 for clinical guidelines for the management of QT prolongation.

Non-hematologic Toxicity

Grade 3 or 4 related to quizartinib and persisting >48 hours without improvement to ≤Grade 2.

- Dosing will be interrupted for up to 14 days.

- If toxicity improves to ≤Grade 1 within 14 days, treatment may be resumed at the reduced dose.

Myelosuppression

In a subject with CRp or CRi, the dose may be reduced at the Investigator's discretion if:

- The subject has been treated for a minimum of 2 cycles.
- Platelet count is $<100 \times 10^9$/L and ANC is $\leq 1000 \times 10^9$/L.
- Marrow blast count is <5%.
- There is no evidence of extramedullary disease.

Initiation of concomitant treatment with a strong CYP3A4 inhibitor is identified in Appendix 1: List of Potential QT Prolonging Drugs, CYP3A4 Inhibitors/Inducers, and P-glycoprotein Inhibitors/Inducers.

The dose will be reduced one level (60 mg to 30 mg or 30 mg to 20 mg) when treatment with a strong CYP3A4 inhibitor is initiated.

- A subject taking a strong CYP3A4 inhibitor at enrollment will initiate quizartinib administration at 20 mg/day. The dose will be escalated to 30 mg/day at day 16 if the QTcF interval is less or equal to 450 msec prior to or at the day 15 ECG evaluations.

Subjects receiving a reduced quizartinib dose may be re-escalated one level to 30 mg/day or to 60 mg/day except for reductions due to Grade 3 QTcF prolongation. If the dose was reduced for toxicity, all events responsible for dose reduction must have resolved to ≤ Grade 1. If the dose was reduced for a strong CYP3A4 inhibitor, the prior dose of quizartinib may be resumed when the inhibitor is withdrawn.

5.6.4.5.   Quizartinib Dose Interruption for HSCT

If a subject undergoes HSCT, quizartinib should be discontinued 7 days before the start of a conditioning regimen. For subjects randomized to the quizartinib arm who undergo HSCT, treatment with quizartinib may be resumed at 30 to 100 days after the transplant. A window of +7 days will be allowed after day 100. Quizartinib may be restarted if:

- Subject has an ANC $>1 \times 10^9$/L and platelet count $>50 \times 10^9$/L without platelet transfusion support within 1 week, or a platelet count $>25 \times 10^9$/L without platelet transfusion support within 2 weeks prior to first dose.
- Subject does not have (1) active acute, or ≥Grade 3 graft versus host disease (GVHD) or (2) active GVHD therapy (not prophylaxis) initiation within 21 days.

The starting dose of quizartinib post-HSCT should be 30 mg daily unless the subject is receiving a strong CYP3A4 inhibitor, in which case the starting dose should be 20 mg daily. Subjects will dose escalate starting on Day 16 if the QTcF interval is less or equal to 450 msec prior to or at the day 15 ECG evaluations.

5.6.5. Blinding

It is not feasible to blind treatment allocations for individual subjects because of different routes of administration, different treatment schedules and different adverse event profiles between quizartinib and salvage chemotherapy. The primary endpoint of overall survival is a robust endpoint and bias due to lack of blinding should be minimal. To further reduce any potential bias, the Sponsor will not have access to aggregate efficacy data except when data from both treatment (quizartinib) and control (salvage chemotherapy) arms are combined. Data relating to the primary endpoint of survival will be restricted so that the Sponsor will not have access to long- term follow-up data on individual subjects, which begins 30 days after discontinuing study treatment in either treatment arm. Approximately 80% of the planned events are expected to occur during this long-term follow-up period and therefore the Sponsor will be blinded to full data supporting the primary endpoint of the study.

5.6.6. Prior and Concomitant Therapy

All concomitant medications administered from the Screening visit through the 30-Day Follow-up visit or until the start of additional AML therapy will be recorded on the appropriate CRF. Refer to Section 5.6.6.1 for prohibited medications and Section 5.6.6.2 for allowed supportive therapy.

5.6.6.1. Prohibited Medications

For all subjects (quizartinib and salvage chemotherapy): Administration of other antineoplastic agents during the study period is prohibited with the exception of hydroxyurea which is allowed for up to 14 days prior to or for up to 4 days concomitantly with quizartinib or salvage chemotherapy to control the peripheral blast count, up to a maximum dose of 5 g/day.

In subjects receiving quizartinib:

- Concomitant medications that prolong the QT/QTc interval are prohibited except when regarded by the Investigator as essential for subject care.

- Strong CYP3A4 inhibitors should be avoided but are not prohibited although require a quizartinib dose adjustments are required. Weak or moderate CYP3A4 inhibitors, such as fluconazole, may be used without dose reduction.

- Concomitant strong or moderate CYP3A4 <u>inducers</u> are prohibited.

If quizartinib is co-administered with drugs that inhibit P-gp, increased concentrations of quizartinib are possible and caution should be exercised. The co-administration of P-gp inhibitors and inducers with quizartinib should be avoided if possible. 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.

Prohibited medications and foods are listed in Appendix 1: List of Potential QT Prolonging Drugs, CYP3A4 Inhibitors/Inducers, and P-glycoprotein Inhibitors/Inducers.

5.6.6.2. Supportive Care Guidelines

Subjects will receive appropriate best supportive care throughout the study.

5.6.7. Treatment Compliance

Trained medical personnel will administer MEC, and FLAG-IDA in the study site setting. Treatment with quizartinib and LoDAC will be initiated in the clinic. Compliance must be monitored by reviewing the subject's returned study treatment supply at every visit and by completing the drug accountability record.

5.7. Study Variables

5.7.1. Primary Efficacy Variable

The primary efficacy variable is overall survival, defined as the time from randomization until death from any cause. Complete definitions of efficacy variables are given in Section 7.2.

5.7.2. Secondary Efficacy Variable

The secondary variable is EFS, defined as the time from randomization until documented refractory disease, relapse after CRc, or death from any cause, whichever is observed first. Complete definitions of efficacy variables are given in Section 7.2.

5.7.3. Additional Efficacy Variables

Additional efficacy variables will be evaluated as follows:

- Leukemia-free survival is the time from the first documented response (CR, CRp, or CRi) until documented relapse or death from any cause.

- Composite complete remission (CRc) rate is the percentage of subjects achieving a best response of CR, CRp, or CRi.

- Complete remission (CR) rate is the percentage of subjects achieving a best response of CR.

- Duration of composite complete remission (CRc) is the time from the first documented CRc (CR+CRi+CRp) until documented relapse.

- Duration of complete remission (CR) is the time from the first documented CR until documented relapse.

5.7.4. Transplantation rate (bridge to transplant) is the percentage of subjects undergoing HSCT directly following protocol specified treatment with no intervening AML therapy.Safety Variables

Safety will be assessed with physical examinations, vital sign determinations, AE evaluations, 12-lead ECGs, ECOG performance scores, and clinical laboratory tests (hematology, serum chemistry, and urinalysis results).

All AEs reported from Day 1 to the 30-Day Follow-up visit, or to the day of withdrawal of the subject from the study, will be evaluated for clinical significance by the Investigator. An AE will be considered clinically significant if it results in inability to perform usual activities, requires acute medical intervention, or in any other way suggests a significant hazard to the subject. AEs will be graded according to Version 4.03 of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4.03) (http://ctep.info.nih.gov).

5.7.5. Pharmacokinetic and Exposure-response Variables

Pharmacokinetics and Concentration-QTcF Relationship of quizartinib and AC886 will be evaluated. Other exposure-response relationships with efficacy or safety variables may be explored.

5.7.6. Additional Variables

The following will be evaluated:

- FLT3-ITD status and allelic ratio
- Mutations in the kinase and juxtamembrane domains of FLT3-ITD and other mutations known to be associated with AML, determined with bone marrow or whole blood samples
- Pharmacogenomics
- Pharmacoproteomic evaluations

5.7.7. Pharmacoeconomic Variables

Resource utilization will be assessed by evaluating the following parameters:

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

5.8. Study Schedule

The schedule of study activities and assessments for subjects receiving quizartinib is presented in Table 3; the schedule of study activities and assessments for subjects receiving quizartinib after HSCT is presented in Table 4; the schedule of study activities and assessments for subjects receiving salvage chemotherapy is presented Table 5; and the schedule of study activities and assessments after treatment is presented in Table 6.

Table 3 **Schedule of Activities and Assessments for Subjects Receiving Quizartinib**

Activity	Screening (≤14 days from randomi-zation)	Cycle 1				Cycle 2		Cycle 3	Cycle 4 and Subsequent cycles
		D 1	D 2 and D 8 ±1	D 15 ±1	D 16 ±1	D 1 ±3	D 15 ±3	D 1 ±3	D 1 ±3
Written informed consent	X								
Medical and disease history and demographics	X								
Physical examination	X	X	X	X		X	X	X	X
Vital sign determinations	X	X	X	X		X	X	X	X
ECOG performance status evaluation	X	X				X		X	X
Assessment of prior and concomitant medications	X[a]	X	X	X		X	X	X	X
Pregnancy test for women of childbearing potential	X[b]	X[b]							X[b]
Determination of coagulation profile (PT/INTR)	X								
Chest X-rays (posterior/anterior and lateral)	X								
12-lead ECG (triplicate)	X[c]	X[c]	X[c]	X[c]		X[c]		X[c]	X[c]
Clinical laboratory tests (hematology; chemistry; urinalysis)	X	X[d]	X[d]	X[d]		X[d]	X	X[d]	X
MUGA scan or ECHO[e]	X								
Bone marrow aspiration or biopsy	X[f]					X[f]		X[f]	X[f]
Collection of bone marrow and whole blood specimen for central laboratory FLT3 mutation determination and other AML-associated mutations[g]	X								
AE/SAE assessment		X	X	X		X	X	X	X
Collection of plasma samples for PK determinations		X[h]	X[h]	X[h]	X[h]	X[h]		X[h]	
Collection of samples for pharmacogenomics and proteomic determinations[i]		X							
Administration of quizartinib at the study site[j]		X	X	X	X	X		X	
Review of returned study medication and assessment of compliance (Day 8 and subsequently)			X	X		X	X	X	X

See footnotes on the next page

[a] Including medications received within 28 days prior to screening.

[b] Women of childbearing potential must have a negative serum test result (minimum sensitivity 25 IU/L or equivalent units of hCG) at screening and a urine test on Day 1 of Cycle 1 before dosing, and every 3 months during the treatment phase.

[c] Triplicate ECGs to be obtained at screening; on Day 1 of Cycle 1 before dosing and 2, 4 and 6 hours after dosing; on Day 2 and 8 of Cycle 1 before dosing and 2 to 4 hours after dosing; on Day 15 of Cycle 1 before dosing and 2, 4 and 6 hours after dosing; on Day 1 of Cycles 2 and 3 before dosing and 2 to 4 hours after dosing; and on Day 1 of all subsequent cycles with no time restriction. Following dose escalation, triplicate ECG determinations should be performed at least once weekly for 2 weeks to monitor QTcF prolongation.

[d] Obtained before dosing. Clinical laboratory evaluations are detailed in Section 8.6, Table 8.

[e] MUGA scans or ECHO are to be performed at screening on all subjects unless a MUGA scan performed within 1 month of screening revealed LVEF $\geq$45%.

[f] Bone marrow aspiration and biopsy for morphology determination are preferred, but biopsy may be omitted if the aspirate is considered to be adequate. Bone marrow samples are required at screening for central testing (within 14 days prior to randomization; bone marrow examinations outside this window may be acceptable if agreed by the Medical Monitor), on Day 1 of Cycle 2 and Cycle 3, at the early termination/end of treatment visit, and as clinically indicated. Bone marrow assessments will be repeated on Day 1 of each subsequent cycle unless the subject has already achieved CR, CRp, or CRi. In that event, bone marrow testing will be repeated after every 3 subsequent cycles, unless there is evidence of relapse. A central laboratory will review a screening specimen to confirm the diagnosis.

[g] The following specimens must be collected and sent to Genoptix for central analysis. A bone marrow and peripheral blood sample should be obtained at screening (at approximately the same time) for determination of FLT3-ITD status. A bone marrow sample should be obtained at treatment discontinuation or relapse. The sample may also be tested for FLT3 point mutations and mutations in other AML-associated genes.

[h] Blood samples for PK determinations will be collected on Day 1 and Day 15 of Cycle 1 before dosing and 1, 2, 4, 6, and 24 hours after dosing. The 24-hour samples must be collected before quizartinib dosing on Day 2 and Day 16. Samples will also be collected on Day 8 of Cycle 1 before dosing and 2 to 4 hours (taken immediately after ECG) after dosing. Thereafter, samples will be collected before dosing and 2 to 4 hours (taken immediately after ECG) after dosing on Day 1 of Cycles 2 and 3. At each time point, 2 mL of blood will be collected. When an ECG is performed at the same study time point, the PK specimen should be taken immediately afterwards.

[i] If consent is provided, blood sample (Pax gene DNA, Pax gene RNA, and PBMC) and buccal swab on Day 1 of Cycle 1 before dosing.

[j] Quizartinib must be taken at the clinic on Cycle 1: Days 1, 2, 8, 15, and 16; Cycle 2: Day 1; and Cycle 3: Day 1. On other days the subject may take quizartinib at home. Quizartinib should be taken in the morning. Please refer to the dosing guidelines in Section 5.6.4.3 regarding required dose escalation at Day 16 if the subject meets the criteria for dose escalation. A second opportunity for dose escalation is available after the first 28-day cycle if the subject has not achieved a CRc. In addition, subjects who achieved a response (CR, CRi, CRp, or PR) at any time and who subsequently relapsed will be assessed for dose escalation provided they meet the same criteria defined in Section 5.6.4.3.

Table 4 Schedule of Activities and Assessments for Subjects Receiving Quizartinib After HSCT

Activity	Cycle 1 (Post-HSCT)			Cycle 2 and subsequent cycles (Post-HSCT)
	D 1	D 8 ±1	D 15 ±1	D 1 ±3
Physical examination	X[a]	X	X	X
Vital sign determinations	X[a]	X	X	X
ECOG performance status determination	X[a]			X
Assessment of concomitant medications	X[a]	X	X	X
12-lead ECG (triplicate)	X[b]	X[b]	X[b]	X[b]
Pregnancy test for women of childbearing potential	X[c]			X[c]
Clinical laboratory tests (hematology; chemistry; urinalysis)	X[a]	X	X	X
Bone marrow aspiration or biopsy	X[d]			X[d]
Specimen collection for central laboratory assessment of FLT3 mutations using bone marrow	X[e]			
AE/SAE assessment	X	X	X	X
Administration of quizartinib at the study site	X[f]	X[f]	X[f]	
Review of returned study medication and assessment of compliance		X	X	X

[a] Performed before dosing and results reviewed before dosing. Blood draws may be taken previous day.

[b] Triplicate ECGs to be obtained on Day 1 of Cycle 1 post-HSCT before dosing, 2, and 4 hours after dosing; on Day 8 of Cycle 1 post-HSCT; Day 15 of Cycle 1 before dosing (including a determination of whether dose escalation is appropriate); Day 1 of Cycle 2 post-HSCT and all subsequent cycles. Following dose escalation, triplicate ECG determinations should be performed at least once weekly for 2 weeks to monitor QTcF prolongation.

[c] Women of childbearing potential must have a negative urine pregnancy test before the start of study treatment and every 3 months during the treatment phase.

[d] Bone marrow aspiration and biopsy for morphology determination are preferred, but biopsy may be omitted if the aspirate is considered to be adequate. Bone marrow samples are required on Day 1 of Cycle 1 post-HSCT (may be taken within 14 days prior to the first dose of study drug; this window may be extended after consultation with the Medical Monitor), on Day 1 of Cycle 4 and every 3 cycles subsequently, at the early termination/end of study visit, and as clinically indicated.

[e] A bone marrow sample should be obtained at Day 1 Cycle 1 (may be taken with 14 days prior to dosing) for central determination of FLT3 mutations and mutations in other genes. FLT3 test result is not required to start quizartinib following transplantation.

[f] Quizartinib should be taken in the morning.

Table 5   Schedule of Activities and Assessments for Subjects Receiving Salvage Chemotherapy

Activity	Screening (≤14 days from random-ization)	Cycle 1				Cycle 2	
		D 1	D 2 and D 8 ±1	D 15 ±3	D 29 ±14	D 1 ±3	D 15 ±3
Written informed consent	X						
Medical and disease history and demographics	X						
Physical examination	X	X	X	X		X	X
Vital sign determinations	X	X	X	X		X	X
ECOG performance status determination	X	X		X		X	X
Assessment of prior and concomitant medications	X[a]	X	X	X		X	X
Pregnancy test for women of childbearing potential	X[b]	X[b]					
Determination of coagulation profile (PT/INR)	X						
Chest X-rays (posterior/anterior and lateral)	X						
12-lead ECG (triplicate)	X[c]	X[c]	X[c]	X[c]		X[c]	X[c]
Clinical laboratory tests (hematology; chemistry; urinalysis)	X[d]	X[d]	X[d]	X[d]		X[d]	X[d]
MUGA scan or ECHO	X[e]					X[e]	
Bone marrow aspiration or biopsy	X[f]				X[f]		
Collection of bone marrow and whole blood specimen for central laboratory FLT3 mutation determination and other AML-associated mutations	X[g]						
AE/SAE assessment		X	X	X		X	X
Collection of samples for pharmacogenomic and proteomic determinations		X[h]					
Administration of MEC or FLAG-IDA at the study site		X[i]					
Administration of low dose cytarabine (LoDAC)		X[j]					

See footnotes on the next page

[a] Includes medications received within 28 days prior to screening.

[b] Women of childbearing potential must have a negative serum test result (minimum sensitivity 25 IU/L or equivalent units of hCG) at screening and a urine test on Day 1 of Cycle 1 before dosing and every 3 months during the treatment phase.

[c] Obtained before dosing. Subjects receiving MEC or LoDAC will undergo ECGs on Day 1 of each cycle; FLAG-IDA will undergo ECGs on Day 2 of each cycle instead of Day 1. All salvage chemotherapy subjects will have ECG on Days 8 and 15 Cycle 1 and Day 15 Cycle 2.

[d] Obtained before dosing. Clinical laboratory evaluations are detailed in Section 8.6, Table 8.

[e] MUGA scans or ECHO are to be performed at screening unless a MUGA scan performed within 1 month of screening revealed LVEF $\geq$ 45%. Subjects receiving FLAG-IDA should have a MUGA scan or ECHO before dosing on Day 1 of Cycle 2, to determine their eligibility for a second cycle.

[f] Bone marrow aspiration and biopsy for morphology determination are preferred, but biopsy may be omitted if the aspirate is considered to be adequate. Bone marrow samples are required at screening (within 14 days prior to randomization; bone marrow examinations outside this window may be acceptable if agreed by the Medical Monitor). For high intensity chemotherapy (MEC or FLAG-IDA), bone marrow samples are also required on Day 29 ($\pm$ 14 days) of each cycle of therapy, and at the early termination/end of treatment visit, and as clinically indicated. For LoDAC, bone marrow samples are also required on Day 1 of Cycle 2 and Day 1 of Cycle 3. If a subject continues to receive LoDAC past Cycle 2, bone marrow assessments will be repeated on Day 1 of each subsequent cycle unless the subject has already achieved a CR, CRp, or CRi. In that event, bone marrow testing will be repeated after every 3 subsequent cycles, unless there is evidence of relapse. Additionally for LoDAC, bone marrow samples are required at the early termination/end of treatment visit, and as clinically indicated.

[g] A bone marrow and peripheral blood sample should be obtained at screening (at approximately the same time) for determination of FLT3-ITD status. A bone marrow sample should be obtained at treatment discontinuation or relapse. The sample may also be tested for FLT3 point mutations and mutations in other AML-associated genes.

[h] If consent is provided, blood sample (Pax gene DNA, Pax gene RNA, and PBMC) and buccal swab on Day 1 of Cycle 1 before dosing.

[i] Additional study site visits are required for subjects receiving MEC (Days 1 through 5) or FLAG-IDA (Days 1 through 6). MEC and FLAG-IDA are administered for up to 2 cycles, depending on response and safety assessments.

[j] Treatment with LoDAC may continue past Cycle 2 and subsequent cycles will follow same procedures as Cycle 2. . Low dose cytarabine should be administered for 10 days in a 28 day cycle in the clinic unless arrangements can be made for administration outside of the clinic. If dosed outside the clinic, a review of medication returned and assessment of compliance must be conducted at the beginning of each cycle.

Table 6   Schedule of Activities and Assessments After Treatment

Activity	End of Treatment Visit[a]	Cross-Over[f]	30-Day Follow-Up	Long-term Follow-Up	Early Termination / End of Study[h]
Written informed consent		X			
Physical examination	X[b]	X			
Vital sign determinations	X[b]	X			
ECOG performance status determination	X[b]	X			
Assessment of concomitant medications	X	X	X		X
Serum pregnancy test for women of childbearing potential	X				
Determination of coagulation profile (PT/INR)		X			
12-lead ECG (triplicate)	X	X			
Clinical laboratory tests (hematology; chemistry; urinalysis)	X[b]	X[g]			
Bone marrow aspiration or biopsy	X[c]				
Assessment of FLT3 mutations using bone marrow	X[d]				
Collection of blood for pharmacogenomic and proteomic determinations	X[e]				
AE/SAE assessment	X	X	X[h]		X
Review of returned study medication and assessment of compliance, for subjects receiving quizartinib or LoDAC	X				X[j]
Determination of remission status, subsequent antileukemic treatments and their outcomes, and survival		X	X[h]	X[i]	
Reason for withdrawal					X

[a] The end of treatment visit should occur within 7 days of the last dose of quizartinib. If quizartinib is discontinued a form must be completed so subject can proceed to HSCT. Additionally subjects moving onto HSCT must have the 30 Day Follow-up phone contact and will be evaluated in Long-Term Follow-up schedule until they resume quizartinib dosing. For subjects receiving chemotherapy the EOT visit corresponds to Day 29 of the last cycle. Assessment of best response to chemotherapy should be conducted at Day 29 (±14 days) or prior to starting subsequent AML therapy.

[b] These assessments need not be repeated if they were performed at a regularly scheduled visit within 3 days of the end of treatment visit.

[c] Bone marrow aspiration and biopsy to determine response status are preferred, but biopsy may be omitted if the aspirate is considered to be adequate. For subjects receiving chemotherapy the bone marrow and response assessment should be conducted at Day 29 ± 14 days.

[d] FLT3 mutation analysis will be performed for subjects in the quizartinib arm only. A bone marrow sample (or peripheral blood sample if marrow cannot be obtained) should be obtained at the end of treatment for determination of FLT3-ITD status. The sample may also be tested for FLT3 point mutations and mutations in other AML-associated genes.

[e] If consent is provided, collection of blood (Pax gene RNA) at end of treatment visit

[f] Screening procedures can be completed within 3 days of the end of treatment visit to determine that subjects meet inclusion criteria and do not meet exclusion criteria. There is no washout period required between stopping salvage chemotherapy and starting treatment with quizartinib.

[g] For the Cross-over period, only hematology and chemistry samples will be collected. Clinical laboratory tests need not be repeated if they were performed within 3 days at the End of Treatment visit, and 3 days prior to the start of quizartinib treatment.

[h] Telephone contact with the subject is sufficient unless any assessment must be repeated for resolution of treatment-related AEs.

[i] Early Termination/End of Study is for subjects withdrawing consent, discontinuing treatment and/or follow up. Review of returned medication is required for subjects receiving study drug at time of withdrawal.

[j] Telephone contact every 3 months.

6. STUDY VISITS AND ACTIVITIES

6.1. Acceptable Windows for Protocol Assessments and Follow-up Visits

Unless otherwise specified in the enrollment criteria, Schedule of Activities table, and in other sections of the protocol, Table 7 serves as a general guideline for acceptable windows within which assessments and procedures are conducted and when study visits are scheduled.

Table 7   Windows for Performing Assessments and Scheduling Follow-Up Visits

PK Assessments	
Time Points	**Acceptable Window**
Predose	< 60 minutes prior to study drug administration
Start of study drug to < 1 hour postdose	± 5 minutes
1 hour postdose to ≤ 6 hours postdose	± 30 minutes, but the PK samples should be taken as close to the protocol stipulated times as possible
24 hours postdose	□ 3 hour prior to next dose
Study Visits	
Visit/Day	**Acceptable Window**
Pretreatment Visit	Scheduled within 14 days prior to randomization[a]
Cycle 1 Day 1 and 2	No window applies
Cycle 1 Day 8	± 1 day
Cycle 1 Days 15 and 16	± 1 day for Day 15; Day 16 must be the day after Day 15
Cycle 2 Day 1	± 3 days[b]
Cycle 2 Day 15	± 1 day
Cycle 3 Day 1	± 3 days[b]
Ongoing Visits	Every 28 days (± 3 days)[b]; and Day 15 of each cycle (± 1 day)
Early Termination or End of Study	7 ± 1 day from date of final dose of quizartinib or site's knowledge of reason for study discontinuation

a   Bone marrow assessments at Screening can be done within 14 days of randomization; bone marrow examinations outside this window may be acceptable if agreed by the Medical Monitor.

b   The ± 3 day window for Cycle 2 Day 1 and Day 1 of ALL cycles thereafter allows scheduling of necessary assessments (including bone marrow aspirates and/or biopsies), obtaining test results, preparing study drug and dispensing for those subjects receiving subsequent cycles of therapy (refer to Schedule of Activities and its footnotes for exceptions). Despite this window, every effort must be made such that there are no dosing schedule interruptions for subjects on this continuous dosing regimen.

6.2.   Study Visits

6.2.1.   Screening Activities

Eligible subjects will be screened as outlined below. Unless otherwise specified, screening procedures must be completed within 14 days prior to randomization to determine that subjects meet inclusion criteria and do not meet exclusion criteria.

- Written informed consent

- Medical and disease history and demographics

- Physical examination

- Vital sign determinations

- ECOG performance status evaluation

- Assessment of prior and concomitant medications, including medications received within 28 days prior to screening.

- Pregnancy testing; women of childbearing potential must have a negative serum (minimum sensitivity 25 IU/L or equivalent units of hCG).

- Determination of coagulation profile (prothrombin time [PT]/international normalized ratio [INR])

- Chest X-rays (posterior/anterior and lateral)

- 12-lead ECG (triplicate)

- Collection of samples for clinical laboratory tests (hematology, chemistry, and urinalysis)

- MUGA scan or ECHO to be performed at screening on all subjects unless a scan performed within 1 month of screening revealed LVEF ≥45%.

- Bone marrow aspiration and biopsy for central confirmation of diagnosis; biopsy may be omitted if the aspirate is considered to be adequate. If a specimen has been sent for central testing but the subject requires treatment for AML before the central FLT3-ITD test result is available, a local test result may be acceptable for randomization after consultation with the Medical Monitor. A Screening specimen must be sent to the central laboratory for confirmation, and results compared to the local test result.

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

- Collection of bone marrow specimen and whole blood (at approximately the same time) for FLT3-ITD testing (and other AML associated mutations) by central laboratory. If it is not feasible to obtain a bone marrow specimen at Screening, peripheral blood only may be submitted to Navigate BioPharma Services, Inc, a Novartis Company (Navigate).

   o This test is approved by the FDA for investigational use and is CE marked. It is not approved by the FDA or other regulatory agencies for commercial use. The results of the test will be used to support the development of a commercial companion diagnostic test. The FDA has reviewed the methodology and assay development and validation of the companion diagnostic test, as documented by Investigational Device Exemption number G140012.

6.2.2. Schedule of Activities and Assessments for Subjects Receiving Quizartinib

6.2.2.1. Cycle 1, Day 1

The following activities will take place during this visit:

- Physical examination

- Vital sign determinations

- ECOG performance status evaluation

- Assessment of prior and concomitant medications

- A urine pregnancy test must be performed prior to dosing and every 3 months during the treatment phase in women of child-bearing potential

- 12-lead ECG (triplicate) before dosing and 2, 4, and 6 hours after dosing

- Collection of samples obtained before dosing for clinical laboratory tests (hematology, chemistry, and urinalysis)

- AE/SAE evaluation

- Collection of blood samples for PK determinations before dosing and 1, 2, 4, and 6 hours after dosing. When an ECG is performed at the same study time point, the PK specimen should be taken immediately afterwards.

- If consent is provided, collection of samples (blood [Pax gene DNA, Pax gene RNA, and PBMC] and buccal swab) should be obtained before dosing for pharmacogenomic and proteomic determinations.

- Administration of quizartinib at the study site

6.2.2.2. Cycle 1, Day 2 and Day 8 (±1 day)

The following activities will take place during these visits:

- Physical examination

- Vital sign determinations

- Review of concomitant medications

- 12-lead ECG before dosing and 2 to 4 hours after dosing

- Collection of samples obtained before dosing for clinical laboratory tests (hematology, chemistry, and urinalysis)

- AE/SAE evaluation

- Collection of blood samples for PK determinations on Day 2 before dosing and on Day 8 before dosing and 2 to 4 hours after dosing. When an ECG is performed at the same study time point, the PK specimen should be taken immediately afterwards.

- Administration of quizartinib at the study site

6.2.2.3. Cycle 1, Day 15 (±1 day)

The following activities will take place during this visit:

- Physical examination

- Vital sign determinations

- Review of concomitant medications

- 12-lead ECG before dosing and 2, 4, and 6 hours after dosing

- ECG review to determine if dose escalation is required:

- Please refer to Section 5.6.4.3 for dosing guidelines to determine if the subject meets specified criteria for dose escalation; first increased dose to be administered Cycle 1 Day 16.

- Collection of samples obtained before dosing for clinical laboratory tests (hematology, chemistry, and urinalysis)

- AE/SAE evaluation

- Collection of blood samples for PK determinations before dosing and 1, 2, 4, and 6 hours after dosing. When an ECG is performed at the same study time point, the PK specimen should be taken immediately afterwards.

- Administration of quizartinib at the study site

- Review of returned study medication and assessment of compliance

6.2.2.4. Cycle 1, Day 16 (the day after Day 15)

The following activities will take place during this visit:

- Collection of blood sample for PK determinations before dosing

- Administration of quizartinib at the study site

6.2.2.5. Cycle 2, Day 1 (±3 days)

The following activities will take place during this visit:

- Physical examination

- Vital sign determinations

- ECOG performance status evaluation

- Review of concomitant medications

- 12-lead ECG (triplicate) before dosing and 2 to 4 hours after dosing

- Collection of samples obtained before dosing for clinical laboratory tests (hematology, chemistry, and urinalysis)

- Bone marrow aspiration and biopsy for local determination of response; biopsy may be omitted if aspirate sufficient.

- AE/SAE evaluation

- Collection of blood samples for PK determinations before dosing and 2 to 4 hours after dosing. When an ECG is performed at the same study time point, the PK specimen should be taken immediately afterwards.

- Administration of quizartinib at the study site

- Review of returned study medication and assessment of compliance

- Consideration of whether a dose escalation is required if it did not occur at Day 16 (following results from bone marrow aspiration and morphology)

6.2.2.6.   Cycle 2, Day 15 (±3 days)

The following activities will take place during this visit:

- Physical examination

- Vital sign determinations

- Review of concomitant medications

- Collection of samples obtained before dosing for clinical laboratory tests (hematology, chemistry, and urinalysis)

- AE/SAE evaluation

- Review of returned study medication and assessment of compliance

6.2.2.7.   Cycle 3, Day 1 (±3 days)

The following activities will take place during this visit:

- Physical examination

- Vital sign determinations

- ECOG performance status evaluation

- Review of concomitant medications

- 12-lead ECG before dosing and 2 to 4 hours after dosing

- Collection of samples obtained before dosing for clinical laboratory tests (hematology, chemistry, and urinalysis)

- Bone marrow aspiration and biopsy for local determination of response; biopsy may be omitted if the aspirate is considered to be adequate

- AE/SAE evaluation
- Collection of blood samples for PK determinations before dosing and 2 to 4 hours after dosing. When an ECG is performed at the same study time point, the PK specimen should be taken immediately afterwards.
- Administration of quizartinib at the study site
- Review of returned study medication and assessment of compliance

6.2.2.8. Cycle 4 and Subsequent Cycles, Day 1 (±3 days)

The following activities will take place during these visits:

- Physical examination
- Vital sign determinations
- ECOG performance status evaluation
- Review of concomitant medications
- A urine pregnancy test must be performed every 3 months during the treatment phase in women of child-bearing potential
- 12-lead ECG (triplicate)
- Collection of samples obtained before dosing for clinical laboratory tests (hematology, chemistry, and urinalysis)
- Bone marrow aspiration and biopsy for local determination of response; (biopsy may be omitted if the aspirate is considered to be adequate) on Day 1 of Cycle 4 unless subject has achieved a CR, CRp or CRi, in which case bone marrow examination should be every 3 cycles subsequently, at the end of treatment/end of study visit, and as clinically indicated
- AE/SAE evaluation
- Review of returned study medication and assessment of compliance

6.2.3. Schedule of Activities and Assessments for Subjects Receiving Quizartinib After HSCT

6.2.3.1. Cycle 1 (Post-HSCT), Day 1

The following activities will take place during this visit:

- Physical examination
- Vital sign determinations
- ECOG performance status evaluation
- Review of concomitant medications
- 12-lead ECG (triplicate) before dosing and 2 and 4 hours after dosing

- Pregnancy testing; women of childbearing potential must have a negative urine pregnancy test result before the start of study treatment and every 3 months during the treatment phase.

- Collection of samples obtained before dosing for clinical laboratory tests (hematology, chemistry, and urinalysis) (blood draws may be performed the prior day; results should be reviewed before dosing)

- Bone marrow aspiration and biopsy for response determination; biopsy may be omitted if the aspirate is considered to be adequate

- Specimen collection for exploratory assessment of FLT3 mutations using bone marrow (or whole blood if marrow cannot be collected); result of FLT3 test not required for subject to start quizartinib.

- AE/SAE evaluation

- Administration of quizartinib at the study site

6.2.3.2.   Cycle 1 (Post-HSCT), Day 8 (±1 day)

The following activities will take place during this visit:

- Physical examination

- Vital sign determinations

- Review of concomitant medications

- 12-lead ECG (triplicate)

- Collection of samples obtained before dosing for clinical laboratory tests (hematology, chemistry, and urinalysis)

- AE/SAE evaluation

- Administration of quizartinib at the study site

- Review of returned study medication and assessment of compliance

6.2.3.3.   Cycle 1 (Post-HSCT), Day 15 (±1 day)

The following activities will take place during this visit:

- Physical examination

- Vital sign determinations

- Review of concomitant medications

- 12-lead ECG (triplicate) before dosing (including a determination of whether dose escalation is appropriate)

- Collection of samples obtained before dosing for clinical laboratory tests (hematology, chemistry, and urinalysis)

- AE/SAE evaluation

- Administration of quizartinib at the study site
- Review of returned study medication and assessment of compliance

6.2.3.4. Cycle 2 and Subsequent Cycles (Post-HSCT), Day 1 (±3 days)

The following activities will take place during these visits:

- Physical examination
- Vital sign determinations
- ECOG performance status evaluation
- Review of concomitant medications
- 12-lead ECG (triplicate)
- Pregnancy testing; women of childbearing potential must have a negative urine pregnancy test result before the start of study treatment and every 3 months during the treatment phase.
- Collection of samples obtained before dosing for clinical laboratory tests (hematology, chemistry, and urinalysis)
- Bone marrow assessment of response by local pathology is required on Day 1 of Cycle 4 and every 3 cycles subsequently, and as clinically indicated
- AE/SAE evaluation
- Review of returned study medication and assessment of compliance

6.2.4. Schedule of Activities and Assessments for Subjects Receiving Salvage Chemotherapy

6.2.4.1. Cycle 1, Day 1

The following activities will take place during this visit:

- Physical examination
- Vital sign determinations
- ECOG performance status evaluation
- 12-lead ECG (triplicate) before dosing for subjects receiving MEC and LoDAC (subjects receiving FLAG-IDA will have triplicate ECGs on Day 2 of each cycle, instead of Day 1)
- Collection of samples obtained before dosing for clinical laboratory tests (hematology, chemistry, and urinalysis)
- A urine pregnancy test must be performed prior to dosing and every 3 months during the treatment phase in women of child-bearing potential
- Review of concomitant medications

- AE/SAE evaluation

- If consent is provided, collection of samples (blood [Pax gene DNA, Pax gene RNA, and PBMC] and buccal swab) obtained before dosing for pharmacogenomic and proteomic determinations

- Administration of MEC or FLAG-IDA at the study site.
  Note: Additional study site visits are required for subjects receiving MEC (Days 1 through 5) or FLAG-IDA (Days 1 through 6). MEC and FLAG-IDA are administered for up to 2 cycles.

- LoDAC should be administered for 10 days in a 28-day cycle in the clinic unless arrangements can be made for administration outside of the clinic. If dosed outside the clinic a review of medication returned and assessment of compliance must be conducted at the beginning of each cycle.

6.2.4.2. Cycle 1, Day 2 and Day 8 (±1 day)

The following activities will take place during these visits:

- Physical examination

- Vital sign determinations

- Review of concomitant medications

- 12-lead ECG (triplicate) before dosing for subjects receiving FLAG-IDA on Day 2. . All chemotherapy subjects will have 12-lead ECGs (triplicate) on Day 8.

- Collection of samples obtained before dosing for clinical laboratory tests (hematology, chemistry, and urinalysis)

- AE/SAE evaluation

- Administration of MEC or FLAG-IDA at the study site.
  Note: Additional study site visits are required for subjects receiving MEC (Days 1 through 5) or FLAG-IDA (Days 1 through 6). MEC and FLAG-IDA are administered for up to 2 cycles.

- LoDAC should be administered for 10 days in a 28-day cycle in the clinic unless arrangements can be made for administration outside of the clinic. If dosed outside the clinic a review of medication returned and assessment of compliance must be conducted at the beginning of each cycle.

6.2.4.3. Cycle 1, Day 15 (±1 day)

The following activities will take place during this visit:

- Physical examination

- Vital sign determinations

- ECOG performance status evaluation

- Review of concomitant medications

- 12-lead ECG (triplicate) before dosing

- Collection of samples obtained before dosing for clinical laboratory tests (hematology, chemistry, and urinalysis)

- AE/SAE evaluation

6.2.4.4.   Cycle 1, Day 29 (± 14 days)

- Bone marrow aspiration and biopsy for determination of response for high intensity chemotherapy (MEC or FLAG-IDA).

6.2.4.5.   Cycle 2, Day 1 (± 3 days)

The following activities will take place during this visit:

- Physical examination

- Vital sign determinations

- ECOG performance status evaluation

- Review of concomitant medications

- 12-lead ECG (triplicate) before dosing for subjects receiving MEC and LoDAC (subjects receiving FLAG-IDA will have triplicate ECGs on Day 2 of each cycle, instead of Day 1)

- Collection of samples obtained before dosing for clinical laboratory tests (hematology, chemistry, and urinalysis)

- MUGA scans or ECHO to be performed in subjects receiving FLAG-IDA before dosing to determine eligibility for a second cycle

- AE/SAE evaluation

- Bone marrow aspiration and biopsy for determination of response for LoDAC. Bone marrow samples are also required Day 1 of Cycle 3. If a subject continues to receive LoDAC past Cycle 2, bone marrow assessments will be repeated on Day 1 of each subsequent cycle unless the subject has already achieved a CR, CRp, or CRi. In that event, bone marrow testing will be repeated after every 3 subsequent cycles, unless there is evidence of relapse.

- LoDAC should be administered for 10 days in a 28 day cycle in the clinic unless arrangements can be made for administration outside of the clinic. If dosed outside the clinic a review of medication returned and assessment of compliance must be conducted at the beginning of each cycle. Treatment with LoDAC may continue past Cycle 2. Subsequent cycles will follow same procedures as Cycle 2.

- Administration of MEC or FLAG-IDA at the study site.
  Note: Additional study site visits are required for subjects receiving MEC (Days 1 through 5) or FLAG-IDA (Days 1 through 6). MEC and FLAG-IDA are administered for up to 2 cycles.

6.2.4.6. Cycle 2, Day 15 (±3 days)

The following activities will take place during this visit:

- Physical examination
- Vital sign determinations
- ECOG performance status evaluation
- Review of concomitant medications
- 12-lead ECG (triplicate) before dosing
- Collection of samples obtained before dosing for clinical laboratory tests (hematology, chemistry, and urinalysis)
- AE/SAE evaluation

6.2.5. Schedule of Activities and Assessments after Treatment

6.2.5.1. End of Treatment Visit

The end of treatment visit should occur within 7 days of the last dose of quizartinib or correspond to Day 29 for the last cycle of salvage chemotherapy. For MEC or FLAG-IDA the end of treatment visit would be Cycle 1 Day 29 or Cycle 2 Day 29.

For subjects on quizartinib who discontinue treatment with the objective of proceeding to HSCT, a quizartinib end of treatment visit should occur. Additionally subjects moving onto HSCT must have a 30 Day Follow-up phone contact. Subsequently, if subject undergoes HSCT, restarts quizartinib and later discontinues treatment, a post-HSCT end of treatment visit should also occur.

The following activities will take place during this visit:

- Physical examination
- Vital sign determinations
- ECOG performance status evaluation
- Review of concomitant medications
- Serum pregnancy testing for women of childbearing potential
- 12-lead ECG (triplicate)
- Collection of samples for clinical laboratory tests (hematology, chemistry, and urinalysis)
- Bone marrow aspiration and biopsy for local response determination are preferred, but biopsy may be omitted if the aspirate is considered to be adequate. For subjects receiving chemotherapy response assessment may be at Day 29 ± 14 days.
- Collection of specimen for exploratory assessment of FLT3 mutations using bone marrow or whole blood will be performed (for subjects in the quizartinib arm only).

- If consent is provided, collection of blood (Pax gene RNA) for pharmacogenomic and proteomic determinations

- AE/SAE evaluation

- Review medication and assessment of compliance

Note: Physical examination, vital sign determinations, ECOG performance status determination, and clinical laboratory tests need not be repeated if they were performed at a regularly scheduled visit within 3 days of the end of treatment visit.

6.2.5.2.   Cross-Over Procedures

In the event that the study outcome demonstrates a clinical benefit to subjects on the quizartinib arm, subjects who were randomized to salvage chemotherapy may be eligible to cross-over to treatment with quizartinib.

Eligible subjects will be screened as outlined below before a subject can cross-over to quizartinib. Unless otherwise specified, screening procedures can be completed within 3 days of the end of treatment visit to determine that subjects meet inclusion criteria and do not meet exclusion criteria.

- Written informed consent

- Physical examination

- Vital sign determinations

- ECOG performance status evaluation

- Assessment of prior and concomitant medications

- Determination of coagulation profile (PT/INR)

- 12-lead triplicate electrocardiogram (ECG)

- Collection of samples for clinical laboratory tests (hematology and chemistry)

- AE/SAE evaluation

- Determination of survival and subsequent antileukemic treatments and their outcomes

Note: Clinical laboratory tests need not be repeated if they were performed within 3 days at the End of Treatment visit, and 3 days prior to the start of quizartinib treatment. There is no washout period required between stopping salvage chemotherapy and starting treatment with quizartinib.

6.2.5.3.   30-Day Follow-Up

The following activities will take place during this visit for subjects on quizartinib or salvage chemotherapy.

For subjects who discontinue quizartinib with the objective of proceeding to HSCT, a quizartinib 30-Day Follow-up visit should occur. Additionally these subjects will be followed in long-term follow-up until they resume quizartinib dosing. Subsequently, if subject undergoes HSCT, takes quizartinib and ends treatment, a post-HSCT 30-Day Follow-up visit should also occur.

For subjects who discontinue salvage chemotherapy and do not qualify for cross-over to quizartinib treatment, a 30-Day Follow-up visit should occur. Additionally these subjects will be followed in Long-Term Follow-up.

Telephone contact with the subject is sufficient unless any assessment must be repeated for resolution of treatment-related AEs:

- AE evaluation; SAE information will be collected at a minimum of 7 days after the end of treatment visit if the subject undergoes HSCT.

- Determination of survival and subsequent antileukemic treatments and their outcomes

- Review of concomitant medications used up to 30-Day Follow-up

6.2.5.4. Long-Term Follow-Up

The following activities will take place during Long-Term Follow-up:

- Determination of survival and subsequent antileukemic treatments and their outcomes, evaluated by telephone contact every 3 months
  - Subjects who stopped quizartinib to move onto HSCT will be followed until they resume quizartinib dosing

- 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 5.4.4 for further details on how subjects will be followed for vital status if they withdraw consent.

6.2.6. Early Termination/End of Study

Every effort should be made to continue to follow subjects after treatment discontinuation including if treatment is declined by the subject. If the subject declines study treatment before receiving any treatment, the reason for declining treatment, and information on any additional AML therapy should be collected. Subjects should continue to be followed at 3 monthly intervals for additional treatment, remission status and survival information.

Subjects withdrawn from the study and study follow up, or who withdraw consent after receiving at least 1 study drug dose should return to the study site for the early termination/end of study visit within 7 days (± 1 day) of the withdrawal decision. The following activities will take place during this visit:

- Review of concomitant medications

- AE/SAE assessment

- Review of returned study medication and assessment of compliance, for subjects receiving quizartinib or LoDAC

Every effort must be made to contact the subject and have him or her return to the study site for the early termination/end of study visit. If the subject cannot return to the site, the reason for and date of termination of the subject's participation in the study must be recorded on the appropriate CRF. If the subject is withdrawn or withdraws consent more than 30 days after study treatment

discontinuation, telephone contact is sufficient and if possible, reason for withdrawal, remission status, and information on any additional AML therapy should be collected.

7.   EFFICACY EVALUATION

Primary Efficacy Variable

The primary efficacy variable is overall survival, 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 censored at the date when they were last known to be alive.

Secondary Efficacy Variable

The secondary variable is EFS, defined as the time from randomization until documented refractory disease, relapse after CRc, or death from any cause, whichever is observed first. Subjects alive without treatment failure or relapse or lost to follow-up at the time of analysis will be censored at the date of their last response assessment.

Additional Efficacy Variables

- Leukemia-free survival is the time from the first documented response (CR, CRp, or CRi) until documented relapse or death from any cause. Subjects alive without relapse or lost to follow-up at the time of analysis will be censored at the date of their last response assessment.

- Composite complete remission (CRc) rate is the percent of subjects achieving a best response of CR, CRp, or CRi.

- Complete remission (CR) rate is the percent of subjects achieving CR.

- Duration of CRc is the time from the first documented CRc (CR + CRp + CRi) until documented relapse. Subjects alive without relapse, lost to follow-up, or who have died without report of relapse as of the time of analysis will be censored at the date of their last response assessment.

- Duration of CR is the time from the first documented CR until documented relapse. Subjects alive without relapse, lost to follow-up, or who have died without report of relapse as of the time of analysis will be censored at the date of their last response assessment.

- Transplantation rate (bridge to transplant) is the percent of subjects undergoing HSCT directly following protocol specified treatment with no intervening AML therapy.

7.1.   Method of Assessment

Bone marrow aspiration and biopsy for morphology are preferred, but biopsy may be omitted if the aspirate is considered to be adequate.

For subjects receiving quizartinib, bone marrow samples are required during Screening (within 14 days prior to the first dose of study drug), Cycle 2 Day 1, Cycle 3 Day 1, at the end of treatment study visit, and as clinically indicated. If the subject has already achieved a CR, CRp, or CRi, bone marrow testing will be repeated after every 3 subsequent cycles. A central laboratory will review the screening specimen to confirm the diagnosis.

For subjects receiving salvage chemotherapy, bone marrow samples are required at screening (within 14 days prior to the first dose of chemotherapy), on Day 29 ± 14 days of Cycle 1, on Day 29 ± 14 days Cycle 2, or as clinically indicated. If a subject continues to receive LoDAC past Cycle 2, bone marrow assessments will be repeated on Day 1 of each subsequent cycle unless the subject has already achieved a CR, CRp, or CRi. In that event, bone marrow testing will be repeated after every 3 subsequent cycles.

7.2. Response Definitions

Response to treatment will be defined per modified Cheson criteria[18] as outlined below.

7.2.1. Complete Remission (CR)

For subjects to be classified as being in CR, they must have bone marrow regenerating normal hematopoietic cells and achieve a morphologic leukemia-free state (<5% bone marrow blasts in bone marrow, no blasts with Auer rods and no persistence of extramedullary disease) and must have an ANC >1×10^9/L and platelet count ≥100×10^9/L and they will be RBC and platelet transfusion independent (defined as 4 weeks without RBC transfusions and 1 week without platelet transfusion).

7.2.2. Complete Remission with Incomplete Platelet Recovery (CRp)

For subjects to be classified as being in CRp, they must achieve CR except for incomplete platelet recovery (<100×10^9/L).

7.2.3. Complete Remission with Incomplete Hematological Recovery (CRi)

For subjects to be classified as being in CRi, they must fulfill all the criteria for CR except for incomplete hematological recovery with residual neutropenia <1×10^9/L and/or platelet count <100×10^9/L. RBC and platelet transfusion independence is not required.

7.2.4.   Partial Remission

For subjects to be classified as being in PR, they must meet the criteria for CRi but only require a decrease of at least 50% in the percentage of blasts in the bone marrow with the total marrow blasts between 5% and 25% inclusive.

7.2.5.   Relapse

Relapse after CR, CRp, or CRi is defined as a reappearance of leukemic blasts in the peripheral blood or ≥5% blasts in the bone marrow aspirate or biopsy not attributable to any other cause or reappearance or new appearance of extramedullary leukemia.

Relapse after PR is similarly defined with reappearance of significant numbers of peripheral blasts and an increase in the percentage of blasts in the bone marrow aspirate to >25% not attributable to any other cause or reappearance or new appearance of extramedullary leukemia.

7.2.6.   Best Response

Best response is defined as the best measured response (CR, CRp, CRi, PR, NR or Unknown) at any time post protocol specified treatment. Response will be assessed by the Investigator and derived per the modified Cheson criteria.

7.2.7.   No Evidence of Response (NR)

For subjects to be classified as being in NR, they must have at least one evaluable bone marrow aspirate or biopsy and not meet the criteria for PR or better. For subjects who do not have evaluable bone marrow aspirate or biopsy, but have presence of leukemic blasts in the peripheral blood, the response is considered as NR.

7.3.   Overall Survival (OS)

Overall survival is the time from randomization until death from any cause.

7.4.   Event-Free Survival (EFS)

Event-free survival is the time from randomization until documented refractory disease, relapse after CRc, or death from any cause, whichever is observed first.

7.5.   Leukemia-Free Survival (LFS)

Leukemia-free survival is the time from the first documented response (CR, CRp, CRi) until documented relapse or death from any cause.

7.6.   Composite Complete Remission (CRc) Rate

Composite complete remission (CRc) rate is the percentage of subjects achieving a best response of CR, CRp, or CRi.

7.7.   Complete Remission (CR) Rate

Complete remission (CR) rate is the percentage of subjects achieving CR.

7.8.   Duration of CRc

Duration of CRc is the time from the first documented CRc (CR+CRp+CRi) until documented relapse.

7.9.   Duration of CR

Duration of CR is the time from the first documented complete remission (CR) until documented relapse.

7.10.   Transplantation Rate

Transplantation rate is the percentage of subjects undergoing HSCT directly following protocol specified treatment with no intervening AML therapy.

8. SAFETY EVALUATION

All subjects receiving at least 1 dose of quizartinib or salvage chemotherapy will be evaluable for safety and defined as the Safety Analysis Set. Safety will be assessed with physical examinations, vital sign determinations, 12-lead ECGs, AE evaluations, and clinical laboratory tests (hematology, serum chemistry, and urinalysis results). The safety data will also be summarized for pre-defined sub-groups.

Study drug toxicity will be assessed continuously. AEs will be evaluated during the study according to NCI CTCAE v4.03 until 30 days after the last dose of study treatment.

Subjects should be instructed to report any new AE or worsening of an existing AE immediately.

8.1. Medical History

Each subject's medical history must be obtained at screening. Information on any prior or existing medical conditions and/or surgical procedures will be recorded on the appropriate CRF.

8.2. Physical Examination

A complete physical examination will be performed at screening to establish a baseline for study entry, and at additional times specified in the study schedule (Section 5.8). Whenever possible, the same individual will perform subsequent examinations to identify changes from baseline. 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.

8.3. Vital Signs

Vital signs, including systolic and diastolic blood pressures, pulse rate, respiratory rate, and body temperature will be determined and recorded at the times specified in the study schedule (Section 5.8). All vital sign measurements should be obtained with subject's supine for at least 5 minutes before determination. Whenever multiple assessments are scheduled at the same time, they should occur in the order of ECGs, vital sign determinations, and blood sample collection.

8.4. Electrocardiograms

Supine triplicate 12-lead ECGs will be obtained at the times specified in the study schedule (Section 5.8). Additional ECGs may be obtained at the Investigator's discretion. Subjects undergoing dose escalation due to lack of response or loss of response after cycle 2 day 1 should be monitored carefully for QT prolongation which should include at least weekly ECGs for 2 weeks.

Electrocardiograms will be recorded in triplicate (3 separate ECGs at least 3 minutes apart but preferably no more than 5 minutes apart; the average of the 3 QTcF determinations will be used to determine safety parameters and dose escalation at Day 16 day of quizartinib administration) and transmitted electronically to a central ECG laboratory. Electrocardiograms will be reviewed by a suitably-qualified physician at the study site to allow immediate decisions about subject safety. When an ECG abnormality of concern is suspected (eg, QTcF >480 msec), the site will

contact the central ECG laboratory to obtain an expedited (within 24 hours) evaluation, and the site will use the central laboratory's analysis for decisions on changes in subject care and protocol compliance. The ECG should be repeated in triplicate within 2 hours on the same day for analysis by the central laboratory. Results of the central ECG laboratory analysis will be the final data for the ECG database. Electrocardiograms will be submitted to the FDA ECG warehouse, if required by the FDA. QTcF duration will be used to make all decisions based on QT criteria.

Guidelines for ECG monitoring are as follows:

- Electrocardiograms will be obtained after the subject has rested quietly and is awake and fully supine for 10 minutes before the first of the triplicate ECGs.

- Additional ECGs can be obtained at any time if clinically indicated. It is important to record actual clock time for each assessment. The triplicate ECGs will be recorded and the average QTcF interval will be determined for each time point.

If clinically significant ECG changes from baseline at screening are noted, the changes will be recorded as AEs on the appropriate CRF. Clinically significant changes will be defined as any ECG variations that are medically significant and could cause a change in medical care. The Investigator must continue to monitor the subject until any ECG changes return to normal.

8.5. Management of QT Prolongation

Quizartinib is known to be associated with prolongation of the QT interval. To reduce the risk of cardiac arrhythmias, it is important to maintain serum electrolytes (K^+, Ca^{++}, and Mg^{++}) within normal range and ideally maintain K^+ above 4.0 mEq/L. Subjects in the quizartinib arm who experience QTcF prolongation ≥ Grade 2 should be managed according to the guidelines below.

- Grade 2 (QTcF average of triplicate readings > 480 msec)

  - Electrolytes (potassium, calcium and magnesium) should be checked and supplementation given to correct any values outside the normal range

  - Concomitant medications should be reviewed to identify and, if appropriate, discontinue any medication with known QT prolonging effects

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

  - Quizartinib dose may be re-escalated after 1 cycle at reduced dose if QT prolongation has decreased to ≤ Grade 1 but subject must be monitored closely for QT prolongation for first cycle at the increased dose.

- Grade 3 (QTcF average of triplicate readings > 500 msec)

  - Electrolytes (potassium, calcium and magnesium) should be checked and supplementation given to correct any values outside the normal range

  - Concomitant medications should be reviewed to identify and, if appropriate, discontinue any medication with known QT prolonging effects

  - Quizartinib dosing will be interrupted for up to 14 days. If QTcF returns to within 30 msec of baseline or ≤450 msec within 14 days, treatment may be resumed at a

reduced dose. Quizartinib dose cannot be escalated following dose reduction for Grade 3 QTcF prolongation.

- Grade 4 (QTcF average of triplicate readings >500 msec or >60 msec change from baseline, and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)

    - Electrolytes (potassium, calcium and magnesium) should be checked and supplementation given to correct any values outside the normal range

    - Concomitant medications should be reviewed to identify and, if appropriate, discontinue any medication with known QT prolonging effects

    - Quizartinib dosing will be permanently discontinued.

Subjects who experience Grade 2 or higher QTcF prolongation and undergo dose interruption and/or reduction must be monitored closely with repeat ECGs to ensure resolution of the QTcF prolongation. QTcF prolongation ≥ Grade 3, either serious or non-serious and whether or not causally related, must be recorded as AE or SAE and reported on a SAE reporting form within 24 hours of awareness, with the investigator's assessment of seriousness, causality, and a detailed narrative.

8.6.   Clinical Laboratory Evaluations

Serum chemistry, urinalysis and hematology tests will be performed at the time specified in the study schedule (Section 5.8). A central laboratory will perform all tests unless this is not feasible, in which case a local laboratory may be used.

The determinations identified in Table 8 will be done.

Table 8   Clinical Laboratory Determinations

Hematology			
Hematocrit	Hemoglobin	Mean corpuscular hemoglobin	Mean corpuscular hemoglobin concentration
Mean corpuscular volume	Platelets	Red Blood Cells	White blood cells (total)
White blood cell differential (% and absolute count)			
Clinical Chemistry			
Albumin	Alanine transaminase	Alkaline phosphatase	Aspartate transaminase
Bicarbonate	Bilirubin, direct	Bilirubin, total	Blood urea nitrogen
Calcium	Chloride	Cholesterol*	Creatine phosphokinase
Creatinine	Gamma-glutamyl transaminase	Glucose	High density lipoprotein*
Lactate dehydrogenase	Lipase	Low density lipoprotein*	Magnesium
Phosphorus	Potassium	Sodium	Total protein
Triglyceride*		Uric acid	
Urinalysis			
Appearance	Bilirubin	Blood	Color
Glucose	Ketones	pH	Protein
Specific Gravity			

*At screening and end of treatment only. Fasting is not required.

8.7.   Pregnancy Testing and Additional Evaluations

Women of childbearing potential must have negative urine or serum pregnancy test results at times specified in the Schedule of Activities (Section 5.8). Follicle stimulating hormone (FSH) may be determined as necessary to confirm postmenopausal status. Serum pregnancy tests and FSH will be performed at the central lab. The central lab will provide the urine pregnancy test kits to be used at the site.

At screening, coagulation profile (PT/INR) will be determined.

8.8.   Adverse Event Definitions

An AE is any untoward medical occurrence in a subject of a clinical investigation, which does not necessarily have a causal relationship to the medicinal product. An AE can therefore be any unfavorable and unintended sign, including an abnormal laboratory finding, symptom, or new or exacerbated disease, whether or not it is considered to be related to the medicinal product. This definition includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of the medicinal product.

Examples of AEs include:

- Exacerbation of a chronic or intermittent pre-existing condition (eg, asthma), including an increase in frequency and/or severity

- New condition (eg, diabetes) detected or diagnosed after administration of the medicinal product, even though it may have been present prior to the start of the study

- Signs, symptoms, or clinical sequelae of a suspected drug interaction

- Signs, symptoms, or clinical sequelae of a suspected overdose of either the investigational product or a concomitant medication.

In this study, AEs include post-treatment events only.

The following are not examples of AEs:

- Medical or surgical procedure. The condition necessitating the procedure is an AE.

- Situation without any untoward medical occurrence (eg, hospitalization for social reasons or reasons of convenience; respite care).

- Anticipated day-to-day fluctuations of a pre-existing disease or condition that does not worsen (eg, fluctuation of blood sugar within a certain range).

Adverse events that occur in subjects after they have discontinued quizartinib to undergo HSCT or other treatment for AML and which are recognized as due to transplantation or the additional AML treatment are not required to be recorded. If the subject restarts quizartinib post-HSCT, then all adverse events while receiving quizartinib must be recorded.

8.9.   Serious Adverse Event Definitions

An SAE is any AE, occurring at any study drug dose and regardless of causality, with any of the following outcomes:

- Death

- Life-threatening

  - The term 'life-threatening' refers to an event in which the subject was at immediate risk of death from the reaction as it occurred. It does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.

- Inpatient hospitalization or prolongation of existing hospitalization

  - "Hospitalization" means that the subject has been admitted to a hospital or emergency facility for observation and/or treatment that would not have been appropriate in a physician's office or outpatient setting. Hospital admissions or surgery planned before any study drug is administered are not to be considered AEs unless there is unexpected deterioration of the subject's condition after study drug treatment (eg, surgery must be performed earlier than planned).

  - Complications occurring during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other criteria for seriousness, the complication becomes an SAE.

- If there is doubt whether hospitalization occurred or was necessary, the associated AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that has not worsened is not considered to be an AE.

- Persistent or significant disability/incapacity

  - Disability/incapacity is defined as substantial disruption of a person's ability to perform normal life functions. This definition is not intended to include events of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, influenza, or accidental trauma, which may interfere with or prevent normal life functions but are not substantial disruptions.

- Congenital anomaly/birth defect

- Important medical event

  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization, but that may be considered an SAE when, based on appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency facility or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An SAE requires additional detailed reports and follow-up. Detailed reports must address the Investigator's estimate of causality and whether or not the AE is identified in nature, severity, and frequency in the Investigator's Brochure or in other risk information that has been supplied to the Investigator (expectedness). SAEs must be recorded on the appropriate CRF page.

The terms "serious" and "severe" are not synonymous.

- The term "severe" is used to describe the severity of a specific event (such as a mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as "serious," which is based on the criteria above and is usually associated with events that threaten a subject's life or functioning.

- A severe AE is not always considered serious in a clinical study. An event is considered serious when it meets at least one of the definitions above. For example, nausea lasting several hours may be considered severe but not an SAE. However, a stroke resulting in only minor disability may be considered mild, but would be considered an SAE based on the criteria above.

- Seriousness, not severity, is a guide for defining regulatory reporting obligations.

8.10. Procedures for Recording and Reporting Adverse Events and Serious Adverse Events Recording AEs and SAEs

All AEs spontaneously reported by subjects and/or reported in response to an open question from study personnel, or revealed by observation, physical examination, or other diagnostic procedure, will be recorded on the appropriate CRF. For both serious and non-serious AEs, the Investigator must determine, based on clinical judgment, both the severity of the events and their relationship to study treatment. All Grade 3 or 4 QTcF prolongations (average of triplicate ECG determination by central reading) must be reported to the Sponsor with the investigator's assessment of seriousness, causality, and a detailed narrative. These events, regardless of seriousness, should be reported within 24 hours of Investigator's awareness of the event.

When an AE or SAE occurs, it is the Investigator's responsibility to review all documentation relevant to the event (eg, hospital progress notes; laboratory and diagnostic reports). The Investigator will then record all relevant information regarding the event on the appropriate CRF. All AEs and SAEs must be recorded, regardless of their relationship to study treatment. It is not acceptable for the Investigator to send photocopies of the subject's medical records to the Sponsor in place of proper CRF completion. However, there may be instances when copies of medical records are requested. In such instances, all information identifying the subject will be redacted before their submission.

The Investigator will also attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis, and not the signs or symptoms, should be documented as the AE or SAE.

8.10.1. Disease-specific AEs and SAEs

Disease progression/worsening of AML should not be recorded as an adverse event. However, events associated with disease progression, such as thrombocytopenia, may be recorded as AE.

Death due to disease progression should not be recorded as adverse event or serious adverse event and should be recorded on the outcomes case report form (CRF).

8.10.2. Assessment of Severity

The Investigator must determine the severity of both serious and non-serious AEs, based on clinical judgment. The severity of each AE, including any abnormal laboratory test result, will be determined using CTCAE v4.03. When CTCAE v4.03 criteria do not apply, severity will be defined according to the following criteria:

Mild	The event, sign, and/or symptom is easily tolerated by the subject, causing minimal discomfort and not interfering with normal daily activities (Grade 1)
Moderate	The event causes sufficient discomfort to interfere with normal daily activities (Grade 2)
Severe	The event prevents the subject from performing normal daily activities (Grade 3)

Life-threatening	The event places the subject at immediate risk of death (Grade 4)
Death	The event results in the subject's death (Grade 5)

8.10.3. Assessment of Causality

The Investigator must determine the relationship of each AE and SAE to study treatment. The Investigator will use clinical judgment to determine this relationship. Other causes, such as concurrent medication or illness, other risk factors, and the event's temporal relationship to study treatment, will be considered. The Investigator will also consult the Investigator's Brochure and/or other product labeling information provided by the Sponsor.

There may be situations when an SAE occurs with minimal information for the initial report. However, it is very important that the Investigator assess causality of every SAE before reporting the event. The Investigator may change his or her opinion of causality in light of follow-up information and amend the SAE report. The causality assessment is one of the most important items for regulatory reporting and should not be left undone.

Relationship of an AE or SAE to study treatment will be defined according to the following criteria:

Definite	There is a clear temporal relationship to study treatment, with no other possible cause.
Possible	A temporal relationship to study treatment is not clear, and alternative etiologies are possible.
Not Related	There is no temporal relationship to study treatment, and/or there is evidence of an alternative cause such as a concurrent medication or illness.

All unexpected events are events that are not identified in the Investigator's Brochure.

8.10.4. SAE Reporting

Every SAE occurring during the study, as defined above, must be reported by the Investigator to the Sponsor's designated contact as soon as possible, but no later than within 1 working day from the time when the Investigator becomes aware of the SAE. All SAEs and deaths must be reported, whether or not they are considered to be causally related to study treatment. SAE reporting forms will be provided to each study site. Additionally, QTcF prolongation $\geq$ Grade 3, either serious or non-serious and whether or not causally related must be reported by the Investigator within 24 hours of awareness. The information recorded on these forms will include at least the following:

- Subject number
- Identity of the event
- Study drug name and dose

- Narrative of the event

- Investigator's assessment of the event's severity and relationship to study treatment

- Investigator's name and signature

If serious, unexpected adverse drug reactions occur, the Sponsor will notify the appropriate regulatory agency or agencies and all participating Investigators on an expedited basis.

All SAEs will be monitored until they have resolved or are clearly determined to result from a chronic or intercurrent condition.

In the case of an SAE, the investigator must contact the Sponsor by telephone or fax immediately (within 24 hours of awareness). The investigator should complete and submit an SAE Worksheet containing all information that is required by the Regulatory Authorities to the Sponsor or designee by fax immediately (within 24 hours of awareness).

If the faxing of an SAE Worksheet is not possible or is not possible within 24 hours, the local drug safety contact should be informed by phone. For contact details see the Study Reference Manual for international number access. Please fax or email the SAE Worksheet to:

Novella Clinical Safety Management

US safety hotline: ▆▆▆▆▆▆

US fax number: ▆▆▆▆▆▆

E-mail: ▆▆▆▆▆▆

If there are any questions, or if clarification is needed regarding the SAE, please contact the Sponsor's Medical Monitor or designee (see contact details of key Sponsor's Personnel in the Study Reference Manual). Follow-up information for the event should be sent promptly (within 7 days) as necessary.

The Sponsor or Sponsor's designee will submit expedited safety reports (ie, IND Safety Reports) to the Regulatory Agencies (ie, FDA) as necessary, and will inform the investigators of such regulatory reports. Investigators must submit safety reports as required by their IRB /IEC within timelines set by regional regulations (ie, EU HAs, FDA). Documentation of the submission to and receipt by the IRB / IEC of expedited safety reports should be retained by the site.

The Investigator may contact the Sponsor's Medical Monitor for any other problem related to the safety, welfare, or rights of the study participant (subject/patient).

Full details of the SAE should also be recorded on the medical records and on the CRF.

The following minimum information is required:

- Study number

- Subject number, sex and age

- The date of report

- A description of the SAE (event, seriousness of the event)

- Causal relationship to the study drug

9. PHARMACOKINETICS

Blood samples for measurement of quizartinib and the active metabolite, AC886, plasma concentrations will be obtained from all subjects randomized to receive quizartinib on Day 1 and Day 15 of Cycle 1 before dosing and 1, 2, 4, 6, and 24 hours after dosing. The 24-hour samples must be collected before quizartinib dosing on Day 2 and Day 16. Samples will also be collected on Day 8 of Cycle 1 before dosing and 2 to 4 hours (taken immediately after ECG) after dosing. Thereafter, samples will be collected before dosing and 2 to 4 hours (taken immediately after ECG) after dosing on Day 1 of Cycles 2 and 3. At each time point, 2 mL of blood will be collected. Pre-dose samples should be taken within 0.5 hours before drug administration.

The 1, 2, 4, and 6 hour post dose samples should be taken within ±0.5 hours 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.

Blood sampling, processing, storage and shipment instructions are provided in the lab manual.

10. PHARMACOGENOMICS AND PHARMACOPROTEOMICS

On Day 1, a buccal swab and whole blood samples (Pax gene DNA, Pax gene RNA, and PBMC) will be collected and shipped to a central laboratory. The PGX/PPX samples will be stored for up to 15 years, at which time they will be destroyed. PGX/PPX research may be conducted to explore PK and safety endpoints during this study or after the conclusion of this study. The results of the genetic and proteomic analysis will not be provided to subjects or the Investigator. Any information obtained from the PGX/PPX research will be the property of the Sponsor. Collection of these samples is not mandatory for participation in this study.

10.1. FLT3-ITD Mutation Assay

Of note, a companion diagnostic is being developed by Navigate for the US and European Union (EU) that will allow determination of FLT3-ITD mutation status from blood and/or bone marrow samples. The FLT3-ITD Mutation Assay is a polymerase chain reaction (PCR)-based molecular assay for detecting FLT3-ITD mutations utilizing genomic DNA isolated from blood or bone marrow. The ITD mutation always occurs in exons 14 and 15 of the FLT3 gene, which includes the juxtamembrane domain and the N-terminal part of the kinase domain. This region, when amplified by PCR using a single set of DNA primers that flank the region, yields ITD mutant reaction products that are greater in size than the 330-base pair non-mutant (ITD wild type) product. The FLT3-ITD Mutation Assay uses a fragment size analysis method to resolve and detect the different-sized PCR products by capillary electrophoresis.

11.   PHARMACOECONOMICS

Resource allocation will be summarized and compared between study arms. The following variables will be measured to assess resource utilization in this study:

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

12. DATA QUALITY ASSURANCE

This study will be organized, performed, and reported in compliance with the Sponsor's and the clinical research organization's (CRO's) standard operating procedures and working practice documents, and with ICH guidelines. Compliance will be achieved by study-specific monitoring of study sites, and by regular audits of the CRO's systems for handling, reporting, and archiving data.

The CRFs will be compared to source documents and reviewed at the study site for completeness by a clinical monitor. If necessary, the study site will be contacted for corrections and/or clarification. All data will be maintained in a study data base for analysis and reporting. Data captured electronically will be electronically transferred to the database. The database will receive a quality assurance check to ensure acceptable accuracy and completeness.

13. STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

13.1. General Considerations

This study is designed to compare the effect or quizartinib monotherapy and salvage chemotherapy on overall survival in subjects with FLT3-ITD(+) AML that is refractory or relapsed within 6 months after first-line therapy with or without consolidating HSCT.

13.2. Subject Disposition, Demographics, and Drug Administration

An accounting of all subjects randomized to the study will be reported. Demographics, disposition including reasons for withdrawal, administration of quizartinib and salvage chemotherapy, and major protocol violations will be tabulated and summarized with descriptive statistics for all randomized subjects. Major protocol violations will be identified in listings.

13.3. Sample Size Determination

Calculation of sample size is based on comparison of OS, the primary efficacy endpoint, in the 2 treatment groups (quizartinib and salvage chemotherapy) at a 2-sided significance level of 0.05, assuming that median survival is 3.9 months in the salvage chemotherapy group with an increase to 6 months, in the quizartinib group (hazard ratio 0.65). A total of 280 events (deaths) are necessary to meet a power requirement of 90%, given an interim analysis planned at 140 events (deaths) with O'Brian-Fleming boundary for superior efficacy and a conditional power (CP) of 10% for futility. For the purpose of sample size calculation, subjects are assumed to be accrued at a rate of 19.2 per month with a drop-out rate of 10%. The target accrual is a total of approximately 363 subjects randomized in a 2:1 ratio (242 subjects in the quizartinib group and 121 in the salvage chemotherapy group) over 17 months, to reach required number of events in a reasonable timeframe and to compensate for drop-outs. All calculations for sample size were performed using East® 6.3.

One formal interim analysis will be performed by an independent SAC and evaluated by an independent DMC according to statistical procedures defined a priori. At the interim analysis, the DMC may recommend 3 potential study options: (1) the study should be stopped due to futility; (2) the study should be stopped for superior efficacy in the quizartinib arm; or (3) the study should continue as planned to the total targeted number of 280 events.

It will be impossible to blind treatment allocations for individual subjects because of different treatment administration schedules and adverse events between the 2 study arms. However, the primary endpoint of survival is a robust endpoint and not susceptible to bias resulting from lack of blinding. Additionally, the Sponsor will not have access to aggregate efficacy data except when data from both treatment and control arms are combined. In addition, data relating to the primary endpoint of survival will be restricted so that the Sponsor will not have access to follow up data on individual subjects after 30 days of discontinuing study treatment. Approximately 80% of events will occur in this long term follow up period and so the Sponsor will be blinded to the primary endpoint of the study.

Randomization will be stratified by prior therapy and response, and pre-selected salvage chemotherapy:

Prior therapy and response:

- Relapsed in ≤ 6 months (not post HSCT)

- Refractory

- Relapsed in ≤ 6 months post allogeneic HSCT

Pre-selected chemotherapy, even for subjects subsequently randomized to quizartinib:

- High intensity chemotherapy (MEC; FLAG-IDA)
- Low intensity chemotherapy (LoDAC)

13.4. Primary Efficacy Analysis

Primary efficacy analysis will take place after the required number of events (deaths), 140 events (deaths) at the interim analysis or 280 events (deaths) at the final analysis, has occurred.

The primary efficacy endpoint (OS) analysis will be based on the stratified log-rank test. The stratification factors will be those used for randomization. A non-stratified log-rank test will be used as supportive evidence of efficacy. These analyses will be performed on the intent-to-treat (ITT) analysis data set, consisting of data from all subjects randomized.

Kaplan-Meier methods will be used to estimate OS in each treatment group, both overall and within subsets of subjects defined by the stratification factors. Estimates of median survival will be provided with 95% confidence intervals. Hazard ratio estimates will also be presented.

Overall survival will be censored at the last date when subjects were known to be alive. For primary analysis, overall survival will not be censored at the time of subsequent non protocol AML therapy, including transplantation.

Sensitivity analyses of OS will be performed by implementing an additional censoring rule: censoring at the date of HSCT for all subjects who have undergone HSCT. The sensitivity analyses will be described in detail in the statistical analysis plan. The primary efficacy analysis will be repeated for the per protocol set (PPS), which includes all subjects who are randomized and have no major protocol deviations.

Protocol deviations will be reviewed in a blinded fashion and categorized as major or minor before the interim analysis and data base lock and will be documented in a memo.

13.5. Secondary Efficacy Analysis

The secondary efficacy endpoint of EFS will be analyzed using the stratified log-rank test with covariates to control for response to first-line AML therapy and pre-selected salvage chemotherapy in the ITT. To maintain the overall type 1 error rate at the 0.05 significance level, hypothesis testing in the secondary analysis will be performed only if the null hypothesis in the primary analysis is rejected at the overall two-sided 0.05 significance level.

Analysis of the secondary efficacy endpoint will be repeated for the PPS.

13.6. Sub-group Analyses

The primary efficacy endpoint (OS) and secondary efficacy endpoint (EFS) will be analyzed for each sub-group defined according to the following:

- Age (<60, and ≥60 years)
- Age (<65 years, ≥ 65 to <75 years, and ≥ 75 years)
- Sex at birth (male, and female)

- Race (White, Black or African American, Asian, and Other)

- Ethnicity (Hispanic or Latino, Non-Hispanic or Latino)

- Geographical region (North America, Europe and Australia, and Rest of World)

- Stratification factors from randomization (response to prior therapy and pre-selected salvage therapy, separately)

- FLT3-ITD allelic burden (using central testing) at randomization >50%, >25% to ≤50%, and ≤25%)

- De novo AML and secondary AML

- Prior allogeneic HSCT (yes and no)

- AML cytogenetic risk score (favorable, intermediate, unfavorable, and unknown risk)

- Blast count at baseline (less than median and greater than or equal to median)

13.7.   Additional Efficacy Analyses

Statistical analyses of exploratory efficacy endpoints include:

- Kaplan-Meier analysis of duration of CRc and CR

- Cochran-Mantel-Haenszel (CMH) test of CR rate

- CMH test of CRc rate

- CMH test of transplantation rate

13.8.   Safety Analysis

The safety analysis set (SAF) includes all subjects receiving at least 1 dose of study treatment (quizartinib or salvage chemotherapy).

Safety evaluation will be based mainly on AEs, clinical laboratory test results, physical examination results, vital signs, ECG results and ECOG performance scores. Descriptive statistics will be used to summarize safety data. All safety data will be summarized by treatment.

All summaries of AEs will include only treatment-emergent events unless otherwise stated. Adverse events will be categorized by system organ class and preferred term using the most current MedDRA dictionary, and will be graded according to NCI CTCAE v4.03.

Additional safety analysis for subjects in post-HSCT quizartinib arm may be performed.

The safety data will also be summarized for each sub-group defined according to the following:

- Age (< 60 and ≥60 years)

- Age (<65, ≥65 to <75, and ≥75 years)

- Sex at birth (male and female)

- Race (Caucasian, Black or African American, Asian, and Other)

- Ethnicity (Hispanic or Latino, Non-Hispanic or Latino)

- Concomitant use of strong CYP3A4 inhibitor (yes and no)

- Baseline ECOG performance score (0, 1, ≥2)

- Baseline body mass index (<18.5, 18.5 to <25, 25 to <30, ≥30 kg/m^2)

- Prior allogeneic HSCT (yes and no)

13.9.   Additional Analyses

Pharmacogenomic analyses are described in Section 10, and pharmacoeconomic analyses in Section 11.

13.10.   Interim Analysis

The study design provides for one formal interim analysis when 50% (140) of the final number of events have been observed. At the discretion of the DMC, one of the following recommendations will be made at this interim analysis:

- Termination of the study for futility.

- Termination of the study for efficacy.

- Continuing the study as planned.

The DMC may only recommend that the Sponsor discontinue the study early only for either efficacy or futility.

The efficacy boundary will be based on the O'Brien-Fleming efficacy boundary derived from the Lan and DeMets error spending function, and the appropriate amount of α will be spent to ensure that the overall 1-sided type1 error remains at 0.025. The futility boundary will be based on CP. At the time of the interim analysis, should the CP cross the futility boundary of 10%, the DMC will decide whether to recommend stopping the study. This decision will be based on the totality of information available at the interim analysis, including results of sensitivity analyses, secondary efficacy endpoint analyses, safety analyses, and benefit-risk analyses.

13.11.   Statistical Methods for Pharmacokinetics and Exposure-response Analyses

Pharmacokinetic parameters for quizartinib and AC886 will be estimated for subjects from whom sufficient plasma samples have been obtained on Day 1 and Day 15 of Cycle 1. Parameters to be calculated will include area under the concentration-time curve (AUC), maximum plasma concentration (C_{max}), minimum plasma concentration (C_{trough}), and time to maximum plasma concentration (t_{max}). Standard non-compartmental analyses will be performed.

Plasma concentrations and PK parameters will be summarized using descriptive statistics, including number of subjects, mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation (CV) of the mean and geometric mean. The time course of drug concentrations will be plotted as appropriate. The relationship between PK parameters and intrinsic (sex, age, race, weight, etc.) or extrinsic (concomitant medications, etc.) factors may be evaluated.

Population PK modeling will be performed for quizartinib and AC886 using nonlinear mixed effects methodology. Data from this study may be pooled with data from other studies for analysis. A covariate analysis will be performed to relate the effects of intrinsic and extrinsic subject factors to exposure.

The relationship between PK parameters and QTc intervals will be examined for quizartinib and AC886 using linear or nonlinear mixed effects methodology. Data from this study may be pooled with data from other studies for analysis. A covariate analysis may be performed to relate the effect of intrinsic and extrinsic subject factors to QTc.

Exploratory assessment of exposure-response relationships will be performed. Data from this study may be pooled with data from other studies for analysis.

14.   ADMINISTRATIVE REQUIREMENTS AND PROCEDURES

14.1.   Institutional Review Board/Independent Ethics Committee Approval

This protocol and the subject informed consent form (ICF) must be reviewed and approved by an IRB/IEC complying with the requirements of 21 CFR Part 56 and local regulatory requirements before subject enrollment at each site. The letter or certificate of approval from the IRB/IEC must be received by the Sponsor or its designee prior to delivery of clinical supplies. The IRB/IEC will be notified of any SAE or suspected unexpected serious adverse reaction in accordance with local regulatory requirements.

14.2.   Ethical Conduct of the Study

This study was designed and will be conducted, and results will be recorded and reported, in compliance with the principles of Good Clinical Practice (GCP). These requirements are stated in US federal regulations (21 CFR Parts 50, 54, 56, and 312) as well as the ICH E6 document titled "Guideline for Good Clinical Practice". State, local, and federal regulations must be followed in the conduct of this study.

14.3.   Changes to the Conduct of the Study or Protocol

No change to the protocol should be initiated without prior written IRB/IEC approval, except when necessary to eliminate an immediate hazard to a subject, or when the change involves only logistic or administrative aspects of the study. Only the Sponsor may initiate protocol amendments.

14.4.   Study Monitoring

A representative of the Sponsor or its designee will visit study sites periodically to monitor the progress of this study in accordance with GCP. It is the Investigator's responsibility to be present or available during monitoring visits. During these routine visits, all data pertaining to a subject's participation in the study must be available to the monitor.

14.5.   Data Management

Data management will be coordinated by the Sponsor in accordance with the standard operating procedures (SOPs) for data management. All study specific processes and definitions will be documented by Data Management. An electronic data capture (EDC) system will be used to collect the clinical study data. Coding of medical terms will be performed using MedDRA and WHO Drug.

14.6.   Investigator Responsibilities

14.6.1.   Informed Consent

Written informed consent from study subjects is required prior to their enrollment in the study. It is the Investigator's responsibility to obtain such consent. Investigators must comply with

21 CFR Part 50, the ICH Guideline for Good Clinical Practice, and all local requirements as applicable when developing ICFs.

Investigators must provide the Sponsor or its designee with a photocopy of the proposed ICF prior to submitting this form to the IRB/IEC. Upon approval of the ICF by the IRB/IEC, Investigators must provide the Sponsor or its designee with a copy of the approved ICF and the IRB/IEC letter of formal approval.

14.6.2.   Case Report Forms

Study data will be collected on electronic CRFs (eCRFs). Incomplete eCRF entries will be referred to Investigators for clarification.

14.6.3.   Subject Confidentiality

Data collected during this study may be used to support the development, registration or marketing of quizartinib. The Sponsor or its designee may request copies of pertinent study-related records, such as subjects' charts and laboratory data, with due precautions for protecting subjects' privacy.

The Sponsor and its designee will comply with all relevant data protection laws in the collection of data from this clinical study. Subjects' names and other identifying information, such as Social Security numbers, will not be disclosed outside study sites. A unique number will be used to identify each subject. Some information, such as laboratory test results, will be kept in a coded form and not attached to subjects' names during the study. The code will be stored in a secure area, and only the study site staff will have access to it.

After subjects have consented to take part in the study, their medical records and the data collected during the study may be reviewed by representatives of the Sponsor, its designees, regulatory authorities, and persons acting on behalf of these agencies, to perform quality assurance audits and to confirm that the data collected are accurate for the purpose of analyzing the results. Personnel of the IRB/IEC and the Quality Assurance Office for Clinical Trials may also review the data to ensure that the study is safe and well managed. These records and data may additionally be reviewed by interested commercial parties. The results of this study may be used in countries throughout the world.

14.6.4.   Record Retention

Investigators must retain study drug disposition records, copies of CRFs, and source documents for the maximum period required by applicable regulations and guidelines or study site procedures, or for the period specified by the Sponsor, whichever is longer. Investigators must contact the Sponsor prior to destroying any records associated with the study. The Sponsor will notify Investigators when the study records are no longer needed. If an Investigator withdraws from the study, the records will be transferred to a mutually agreed upon designee, such as another Investigator or the IRB/IEC. Notice of such transfer will be given in writing to the Sponsor.

14.7. Protocol Deviations

Protocol deviations include all important deviations related to study inclusion or exclusion criteria, study conduct, subject management, or subject assessment. Major protocol deviations must be reported to the Sponsor or its designee and to the IRB/IEC. Examples of protocol deviations include:

- Randomization of subjects not satisfying entry criteria
- Failure to withdraw subjects meeting withdrawal criteria
- Administration of the wrong treatment or an incorrect study drug dose

14.8. Control of Materials

14.8.1. Receipt of Clinical Supplies

Shipment of quizartinib from the Sponsor or designee to Investigators will be accompanied by a clinical supply shipment and receipt verification form, which will describe the dosage form and the amount of clinical supplies provided for the study. Investigators must ensure that study drug is maintained in a secure area with restricted access.

14.8.2. Disposition of Unused Clinical Supplies

A clinical supply reconciliation form must be completed by each Investigator or designee upon completion or termination of the study. All unused clinical supplies will be recorded in the drug dispensing and accountability record for quizartinib and on the clinical supply reconciliation form, and will be destroyed at study sites following approved procedures, or returned to the Sponsor, after completion of the study.

14.9. Financial Disclosure

Principal Investigators, and all sub-investigators listed on FDA Form 1572, will provide the Sponsor or designee with information on any financial interests in the Sponsor held or received by them, their spouses, or dependent children, in accordance with US federal law (21 CFR Part 54). This disclosure must be made at the time of each Investigator's first involvement in the study, throughout the study, and for 1 year after study completion.

14.10. Publication Policy

This is a multi-site study, and results from an individual site will not be published before the first multi-site publication by the Sponsor. If there is no multi-site publication within 18 months after the study has been completed or terminated at all sites and all data have been received, an individual site will have the right to publish its results, subject to the following requirements. Prior to submitting or presenting a manuscript or other study-related material to a publisher, reviewer, or other external party, the Investigator or site will provide the Sponsor with a copy of the manuscript or other material, and the Sponsor will have 60 days from receipt of the material to review it and comment. At the Sponsor's request, the Investigator or site will remove any confidential information, other than study results, prior to submitting or presenting the material. The Investigator or site will, at the Sponsor's request, further delay publication or presentation

for up to 120 days, to allow the Sponsor to protect its interests in any of its inventions described in the material.

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APPENDIX 1: LIST OF POTENTIAL QT PROLONGING DRUGS, CYP3A4 INHIBITORS /INDUCERS, AND P-GLYCOPROTEIN INHIBITORS/INDUCERS

This appendix lists medications that potentially prolong QT/QTc and medications and foods that are common inhibitors of CYP3A4. This list should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity to prolong QT/QTc and/or inhibit CYP3A4.

Potential QT/QTc Prolonging Drugs

Drug Type	Generic Drug Name
Class IA antiarrhythmics	quinidine procainamide disoppyramide
Class IC antiarrhythmics	flecainide propafenone moricizine
Class III antiarrhythmics	amiodarone sotalol bretylium ibutilide dofetilide
Antipsychotics	thioridazine mesoridazine chlorpromazine prochlorperazine trifluoperazine fluphenazine perphenazine pimozide risperidone ziprasidone lithium haloperidol
Tricyclic/tetracyclic antidepressants	amitriptyline desipramine doxepin dosulepin hydrochloride imipramine maprotiline
Selective serotonin and norepinephrine reuptake inhibitors (SSNRIs)	venlafaxine
Macrolide antibiotics	azithromycin erythromycin

	clarithromycin dirithromycin roxithromycin tulathromycin
Fluoroquinolone antibacterials	moxifloxacin gatifloxacin
Azole antifungals	ketoconazole fluconazole itraconazole posaconazole voriconazole
Antimalarials	amodiaquine atovaquone chloroquine doxycycline halofantrine mefloquine proguanil primaquine pyrimethamine quinine sulphadoxine
Antiprotozoals	pentamidine
Antiemetics	droperidol dolasetron granisetron ondansetron
Antiestrogens	tamoxifen
Immunosuppresants	tacrolimus

CYP3A4 Inhibitors

Inhibitor Type	Generic Drug Name	Comments
Strong	boceprevir clarithromycin conivaptan grapefruit grapefruit juice indinavir itraconazole ketoconazole lopinavir mibefradil nefazodone nelfinavir posaconazole ritonavir saquinavir telaprevir telithromycin voriconazole	**Use prohibited for subjects receiving quizartinib unless necessary for patient care in which case a dose reduction of quizartinib is required**
Moderate	amprenavir aprepitant atazanavir ciprofloxacin crizotinib darunavir diltiazem erythromycin fluconazole fosamprenavir imatinib verapamil	**Use allowed. No requirement for quizartinib dose reduction**
Weak	alprazolam amiodarone amlodipine atorvastatin bicalutamide cilostazol cimetidine cyclosporine fluoxetine fluvoxamine ginkgo goldenseal isoniazid lapatinib oral contraceptives	**Use allowed. No requirement for quizartinib dose reduction**

	nilotinib pazopanib ranitidine ranolazine ticagrelor tipranavir zileuton	

CYP3A4 Inducers

Inducer Type	Generic Drug Name	Comments
Strong	avasimibe carbamazepine phenytoin rifampin St. John's wort	**Use prohibited for subjects receiving quizartinib**
Moderate	bosentan efavirenz etravirine modafinil nafcillin	**Use prohibited for subjects receiving quizartinib**
Weak	amprenavir aprepitant armodafinil clobazam echinacea pioglitazone prednisone rufinamide vemurafenib	**Use allowed.**

P-glycoprotein Inhibitors/Inducers

Inhibitors	Inducers
Amiodarone Azithromycin Captopril Carvedilol Clarithromycin Conivaptan Cyclosporine Diltiazem Dronedarone Erythromycin Felodipine Itraconazole	Avasimibe Carbamazepine Phenytoin Rifampin St. John's wort Tipranavir/ritonavir

Ketoconazole Lopinavir Ritonavir Quercetin Quinidine Ranolazine Ticagrelor Verapamil	