CLINICAL STUDY PROTOCOL

A PHASE 1 STUDY OF MILADEMETAN IN COMBINATION WITH QUIZARTINIB IN SUBJECTS WITH FLT3-ITD MUTANT ACUTE MYELOID LEUKEMIA THAT ARE RELAPSED/REFRACTORY, OR NEWLY DIAGNOSED AND UNFIT FOR INTENSIVE CHEMOTHERAPY

DS3032-A-U105

IND NUMBER: 135361
EudraCT NUMBER: 2019-001344-22

VERSION 5.0, 27 AUG 2019
VERSION 4.0, 01 APR 2019
VERSION 3.0, 11 OCT 2018
VERSION 2.0 (For Agency Assessment), 12 MAR 2018
VERSION 1.0, 31 JAN 2018

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INVESTIGATOR AGREEMENT

A PHASE 1 STUDY OF MILADEMETAN IN COMBINATION WITH QUIZARTINIB IN SUBJECTS WITH FLT3-ITD MUTANT ACUTE MYELOID LEUKEMIA THAT ARE RELAPSED/REFRACTORY, OR NEWLY DIAGNOSED AND UNFIT FOR INTENSIVE CHEMOTHERAPY

Sponsor Approval:

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

PPD

PPD

Print Name

Senior Director, Global Oncology Research and Development

Title

29 Aug 2019

Date (DD MMM YYYY)

Investigator's Signature:

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

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

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

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

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

Print Name | **Signature**

Title | **Date (DD MMM YYYY)**

SUMMARY OF CHANGES

Amendment Rationale:

The main purposes of this amendment are to allow concomitant administration of strong CYP3A inhibitors with milademetan, to update dosing recommendations of milademetan and quizartinib when concomitantly administered with strong CYP3A inhibitors, to remove the fasting restriction for milademetan outside of the drug-drug interaction (DDI) substudy, and to clarify the efficacy endpoints.

Changes to the Protocol:

Please refer to the comparison document for protocol Version 5.0 (dated 27 Aug 2019) vs. protocol Version 4.0 (dated 01 Apr 2019) for actual changes in-text. The summary of changes below is a top-line summary of major changes in the DS3032-A-U105 clinical study protocol (Version 5.0) by section.

DESCRIPTION OF EACH HIGH-LEVEL CHANGE	
1	Updated objectives and efficacy outcome measure definitions. **The following sections were updated:** Protocol Synopsis (Study Objectives) Section 2 (Study Objectives and Hypothesis) Section 7 (Efficacy Assessments) Section 11.4 (Efficacy Analyses) Section 17.4 (Response Criteria for AML) Section 17.5 (Additional Definitions/Response Criteria) Figure 17.1 (Hematologic Recovery Requirements for CR and CRi) Figure 17.2 (Hematologic Recovery Requirements for CR and CRh)
2	Clarified that study is a first-in-human with 2 investigational agents and that study will be conducted globally. **The following sections were updated:** Protocol Synopsis (Study Design) Section 1.3 (Potential Risks for Study Subjects) Section 3.1 (Overall Design)

DESCRIPTION OF EACH HIGH-LEVEL CHANGE	
3	Updated study sites for dose escalation to include sites in Japan, Asia, and Europe in addition to the United States. The number of study sites was also updated from approximately 10 to approximately 15 for dose escalation, with approximately 15 additional sites to be added as necessary for the dose expansion part. **The following sections were updated:** Protocol Synopsis (Study Sites and Location) Section 3.1 (Overall Design)
4	Added duration of subject participation and of study to align with Synopsis and included a study design table. **The following sections were updated:** Section 3.1 (Overall Design)
5	Updated proposed dose cohorts and schedules in dose escalation. **The following sections were updated:** Protocol Synopsis (Study Design) Section 3.1.2 (Part 1 [Dose Escalation]) Table 3.2 (Proposed Cohorts and Dose Levels of Quizartinib and Milademetan for Dose Escalation)
6	Clarified cohort stopping criteria, updated definition of dose-limiting toxicities (DLTs) and dose interruptions/reductions, and updated expected adverse reactions and risks for quizartinib and milademetan. **The following sections were updated:** Protocol Synopsis (Study Design) Section 1.3 (Potential Risks for Study Subjects) Section 3.1.1 (Dose Limiting Toxicity Definition) Section 3.1.2.1 (Stopping Rules [Dose Escalation]) Section 5.4 (Dose Interruptions and Reductions)

DESCRIPTION OF EACH HIGH-LEVEL CHANGE	
7	Updated dose modification schedule during concomitant use of strong CYP3A inhibitors and due to drug-related myelosuppression. **The following sections were updated:** Protocol Synopsis (Study Design) Section 3.1.2 (Part 1 [Dose Escalation]) Section 3.1.2.2 (Dose Modification of Milademetan due to Thrombocytopenia and/or Neutropenia [Cycle 2 and Later])
8	Updated inclusion criteria to clarify permitted diagnoses and prior therapies for study parts/cohorts, updated Eastern Cooperative Oncology Group (ECOG) Performance Status ranges, unified renal function criteria and total bilirubin criterion across study parts/cohorts, updated the definition of childbearing potential and pregnancy testing requirements, and added required compliance for pharmacogenomics testing. **The following sections were updated:** Protocol Synopsis (Subject Eligibility Criteria) Section 4.1 (Inclusion Criteria) Section 6 (Study Procedures) Section 9.6 (Exposure In Utero During Clinical Studies)
9	Updated exclusion criteria regarding New York Heart Association (NYHA) Class III or IV congestive heart failure, left ventricular ejection fraction, diffusing capacity of the lung for carbon monoxide and forced expiratory volume, and prior hematopoietic cell transplantation. **The following sections were updated:** Protocol Synopsis (Subject Eligibility Criteria) Section 4.2 (Exclusion Criteria)
10	Clarified the sample size determination, removed modified continual reassessment method (mCRM) as a model during dose escalation, and added clarifying details for dosing and model design in dose expansion. **The following sections were updated:** Protocol Synopsis (Planned Sample Size) Section 3.1.2 (Part 1 [Dose Escalation]) Section 3.1.3 (Part 2 [Dose Expansion]) Section 11.10 (Sample Size Determination)

DESCRIPTION OF EACH HIGH-LEVEL CHANGE	
11	Added an allowance to use LVEF value from prior ECHO/MUGA scan. **The following sections were updated:** Section 5.7.1 (Subject Re-screening Procedures) Section 17.3 (Schedule of Events)
12	Updated study procedures to require FSH testing for confirmation of menarche, define length of transfusion history, to clarify on-site administration of study drugs, to require documentation of transfusions, to update required bone marrow sampling for disease and biomarker assessments, to add an additional informed consent for PGx sample storing, to update schedule for banking plasma samples, and to define diagnostic tool for FLT3-ITD mutation assessment. **The following sections were updated:** Section 6.1 (Screening) Section 6.3 (Treatment Period) Section 17.3 Schedule of Events Section 17.7 (Highly Effective Methods of Birth Control) Section 17.8 (FLT3-ITD Mutation Assay)
13	Removed urinalysis from required clinical laboratory test panel. **The following sections were updated:** Protocol Synopsis (Study Endpoints) Section 2.4.1 (Safety Endpoints) Section 6 (Study Procedures) Section 9.7 (Clinical Laboratory Evaluations) Section 11.6 (Safety Analyses) Section 17.3 (Schedule of Events)
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DESCRIPTION OF EACH HIGH-LEVEL CHANGE	
15	Clarified subject re-screening procedures. **The following section was updated:** Section 5.7.4 (Subject Re-screening Procedures)
16	Updated language for ECG measurements and ECHO/MUGA scans. **The following sections were updated:** Section 6 (Study Procedures) Section 17.3 (Schedule of Events)
17	Updated and clarified bone marrow testing requirements and frequency for disease assessment and biomarker testing. **The following sections were updated:** Section 6 (Study Procedures) Section 7.1.1 (Bone Marrow Biopsies/Aspirates) Section 7.1.1.1 (Bone Marrow Samples for Translational Research) Section 17.3 (Schedule of Events) Figure 7.1 (Schedule for Bone Marrow Biopsies/Aspirates)
18	Clarified follow-up phase procedures and added reminder to obtain confirmation of consent to follow-up. **The following sections were updated:** Section 6.4 (End-of-Treatment - Part 1 and Part 2 [Post-cycle]) Section 6.5 (Follow-up Phase Part 1 and Part 2) Section 17.3 (Schedule of Events)
19	Updated address list. **The following sections were updated:** Section 15.10 (Address List)

DESCRIPTION OF EACH HIGH-LEVEL CHANGE	
20	Removed references to pyoderma gangrenosum. **The following sections were updated:** Section 1.3 (Potential Risks for Study Subjects) Section 16 (References) Section 17.3 (Pyoderma Gangrenosum)
21	Added reference tables for ECOG Performance Status Scale and NYHA Functional Classifications. **The following sections were updated:** Section 17.9 (Eastern Cooperative Oncology Group [ECOG] Performance Status) Section 17.10 (New York Heart Association [NYHA] Functional Classification)
22	Minor editorial and formatting changes were made throughout the document.

PROTOCOL SYNOPSIS

EudraCT Number:	2019-001344-22
IND Number:	135361
Protocol Number:	DS3032-A-U105
Investigational Product(s):	milademetan; quizartinib (in combination)
Active Ingredient(s)/INN:	milademetan; quizartinib
Study Title:	A Phase 1 study of milademetan in combination with quizartinib in subjects with FLT3-ITD mutant acute myeloid leukemia that are relapsed/refractory, or newly diagnosed and unfit for intensive chemotherapy
Study Phase:	Phase 1
Indication Under Investigation:	FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) mutant acute myeloid leukemia (AML)
Study Objectives:	**Primary Objectives:** Part 1 (Dose Escalation): To determine the safety and tolerability of the drug combination, identification of the optimum dosing schedule, maximum tolerated dose (MTD), and the recommended dose for expansion cohort (RDE). Part 2 (Dose Expansion): To confirm safety and tolerability of the combination therapy at RDE and to identify the recommended Phase 2 dose. Assessment of efficacy. **Secondary Objectives:** Part 1 only: – Preliminary assessment of efficacy. Part 1 and Part 2: To evaluate the pharmacokinetics (PK) of milademetan, quizartinib, and the active metabolite of quizartinib, AC886. **Outcome Measures**

Primary Outcome Measures

Part 1 only:

Number of subjects with dose limiting toxicities (DLTs).

[Time Frame: Approximately 18 months from start of the study]

Part 1 and Part 2:

Number of subjects who experienced an adverse event (AE) during the study.

[Time Frame: Approximately 3 years from start of study]

Part 2 only:

Number of subjects with response to treatment.

Response to treatment will be assessed using 2017 European LeukemiaNet (ELN) recommendations. These include the rates of complete remission (CR); CR with incomplete blood count recovery (CRi); composite complete remission (CRc); duration of composite complete remission (DOR); morphologic leukemia-free state (MLFS); partial remission (PR); overall response rate (ORR); and stable disease (SD). CR with partial hematological recovery (CRh) will be evaluated separately from the other response criteria.

[Time Frame: Approximately 3 years from start of study]

Secondary Outcome Measures

Part 1 only:

Number of subjects with response to treatment.

Response to treatment will be assessed using 2017 ELN recommendations. These include the rates of CR, CRi, CRc, DOR, MLFS, PR, ORR, and SD. CRh will be evaluated separately from the other response criteria.

[Time Frame: Approximately 18 months from start of study]

Part 1 and Part 2:

Plasma concentrations and PK parameters of milademetan, quizartinib, and AC886.

[Time Frame: Approximately 3 years from start of study]

Study Design:	DS3032-A-U105 is a first-in-human co-development study of 2 investigational agents: milademetan and quizartinib. This will be an open-label, Phase 1 study of milademetan in combination with quizartinib in subjects with FLT3-ITD mutant AML, with a dose escalation part (Part 1) and a dose expansion part (Part 2). Quizartinib will be administered once daily (qd) in 28-day cycles, and milademetan will be administered qd on Days 1 to 14 of each 28-day cycle (qd 14/28) or in alternative dosing schedules. **Part 1 (Dose Escalation):** Dose escalation will assess the safety, tolerability, PK, and preliminary efficacy of increasing doses of milademetan and quizartinib in subjects with FLT3-ITD mutant relapsed/refractory (R/R) AML. The evaluation period for DLTs will be 28 days (Cycle 1) from the start of study drug administration. The dose escalation will be guided by a Bayesian logistic regression model (BLRM) for dual agent combination and governed by the escalation with overdose control (EWOC) principle. The determination of MTD(s) will be guided by the BLRM using accumulated DLT data as well as other safety and PK data. The RDE will be decided based on considerations of the respective MTD(s) guided by the BLRM and on an overall assessment of safety data from all cycles, PK data, and preliminary efficacy data. Cohorts of 3 to 6 subjects will be enrolled and assessed for DLT before escalation to a new higher dose. For a subject to be considered evaluable for DLT, the subject must have received at least 75% of the prescribed Cycle 1 doses and completed safety assessments of the DLT evaluation period, or experienced a DLT in this period. Subjects who started treatment but who do not meet the criteria to be DLT-evaluable will not be included in the BLRM update. In some cases, a subject in the previous cohort may experience a DLT after the enrollment of subjects to a new cohort has begun. In this event, the dose level assignment of the next subject(s) in the new cohort will be based on an updated BLRM using DLT outcome data from all assessed dose cohorts up to that point. A delay of at least 7 days will occur between the first subject dosed and the second subject dosed in the first cohort. If 2 evaluable subjects in any cohort experience DLT before the enrollment of the next subject, the model will be re-evaluated and discussion between the Investigators and Sponsor will occur before enrollment of any additional subjects in the cohort.

Enrollment of subjects to a new cohort requires completion of DLT evaluation of at least 3 subjects treated in the current cohort at the intended dose levels. The Investigator and Sponsor will also assess safety and tolerability on an ongoing basis and will continue dosing if there are no safety or risk/benefit concerns and if the subject is deriving clinical benefit. Additional subjects for the characterization of safety, PK, or PD may be added at any dose escalation cohort below the MTD dose level or at the MTD in parallel with ongoing escalation up to a maximum of 12 subjects in each cohort. Further details can be found in the Cohort Management Plan.

Milademetan Dose Levels

The proposed starting dose of milademetan will be 90 mg, which will be escalated through 120 mg and 160 mg; all 3 doses will follow the qd 14/28 dosing schedule unless the safety data suggest the use of a less frequent dose schedule. Based on emerging safety and efficacy data during dose escalation, the dose levels of milademetan may be evaluated up to 200 mg or 260 mg in alternative dosing schedules with less frequent doses (eg, Days 1 to 7 of each 28-day cycle [qd 7/28] and Days 1 to 3 of each 14 days administered twice in a 28-day cycle [qd 3/14 × 2]). The maximum dose for milademetan will be up to 260 mg in the qd 3/14 × 2 schedule as determined in the DS3032-A-U101 study.

Quizartinib Dose Levels

There are 3 proposed dose levels of quizartinib: 30 mg, 40 mg, and 60 mg. Quizartinib monotherapy from 30 mg to 60 mg doses was demonstrated to be safe and clinically active in the Phase 2 (2689-CL-2004) study. However, the optimal dose/schedule of quizartinib is unknown when it is combined with miladematan. Therefore, 30 mg qd quizartinib will be used as the starting dose, as this dose demonstrated a similar CRc rate as 60 mg qd quizartinib.

If quizartinib is increased to the 60-mg dose level, subjects will be dosed at 30 mg for the first 14 days to evaluate the QT prolongation risk in each subject.

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- escalate dose to 60 mg quizartinib on Day 15 of Cycle 1 and continue at same dose in subsequent cycles

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- continue at 30 mg quizartinib in combination with assigned dose of milademetan, in the absence of other risk factors

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- continue with quizartinib dose reduction of 1 level in combination with assigned dose of milademetan, in the absence of other risk factors
- multiple stepwise dose reductions allowed to mitigate QTcF prolongation risks

QTcF >500 ms, recurring despite dose reductions and correction/elimination of other risk factors

- permanently discontinue from quizartinib

In cohorts with quizartinib 60 mg, it is possible that not all subjects may be assignable to quizartinib 60 mg on Day 15 after the 30 mg lead-in for the first 14 days, and therefore additional subjects may be enrolled for evaluation of the cohorts.

Dose Escalation Plan

The proposed dose levels shown in the following table were chosen based on the safety and preliminary efficacy data from the single agent studies. The dose and schedule of milademetan will be first optimized during dose escalation in combination with 30 mg qd quizartinib. When a decision is made to escalate the dose, the milademetan dose can be escalated to the next dose level at the existing dosing schedule suggested by BLRM (eg, qd 14/28), at a less frequent dosing schedule (ie, qd 7/28 or qd 3/14 × 2), or in separate cohorts of 2 schedules in parallel; the MTD(s) in those schedules may be separately assessed. While the BLRM will provide the dose recommendation, the decision to use a less frequent dose schedule will be taken after discussion between the Investigators and Sponsor based on the overall safety data thus far. However, dose escalation from any dose level in a less frequent dose schedule to a more frequent dose schedule is not allowed.

Once the most optimal dose and schedule of milademetan is identified, the quizartinib qd dose will be escalated from 30 mg to 40 mg, and then from 40 mg to 60 mg, in combination with the optimal dose of milademetan. During dose escalation, simultaneous dose escalation of both agents will not be not allowed. Additional dose combinations not shown in the table may be tested based on emerging safety data during dose escalation.

Proposed Cohorts and Dose Levels of Quizartinib and Milademetan for Dose Escalation

Quizartinib Dose	Milademetan Dose
30 mg qd	90 mg qd 14/28[a]
30 mg qd	120 mg qd 14/28[a]
30 mg qd	160 mg qd 14/28[a]
30 mg qd	200 mg qd 7/28[a]
30 mg qd	260 mg qd 3/14 × 2
40 mg qd	Most optimal dose and schedule identified in combination with 30 mg qd quizartinib
60 mg qd following 30-mg lead-in (14 days)	Most optimal dose and schedule identified in combination with 30 mg qd quizartinib

qd = once daily

[a] At any milademetan dose level, if the evaluated dosing schedule is not tolerated, alternative dosing schedules of less frequent doses (eg, qd 7/28 or qd 3/14 × 2) may be evaluated. However, dose escalation from any dose level in a less frequent dose schedule to a more frequent dose schedule is not allowed.

Note: Some of the cohorts shown in the table may be dropped based on the emerging safety data during dose escalation.

For subjects receiving concomitant therapy with a strong CYP3A inhibitor:

Special considerations are required for subjects receiving concomitant therapy with a strong CYP3A inhibitor.

The following dose reductions will be performed with the concomitant administration of a strong CYP3A inhibitor.

Quizartinib:

- 60 mg dose will be reduced to 30 mg
- 30 mg and 40 mg doses will be reduced to 20 mg
  - Consequently, quizartinib 30-mg lead-in to 60 mg will be reduced to a 20-mg lead-in to 30 mg

Milademetan:

- Dose will be reduced to half of the prescribed dose (ie, 90-mg, 120-mg, and 160-mg doses of milademetan will be reduced to 45 mg, 60 mg, and 80 mg, respectively)

Resumption of regularly scheduled doses of quizartinib and milademetan after discontinuation of the strong CYP3A inhibitor should be as follows:

Quizartinib:

- Resume regularly scheduled dose the day following discontinuation

Milademetan:

- Resume regularly scheduled dose after a 3-day washout period following discontinuation

Dose Limiting Toxicity Definition

A DLT is defined as any non-hematological treatment-emergent adverse event (TEAE) unless incontrovertibly related to disease progression, intercurrent illness, or concomitant medication, that occurs during the DLT evaluation period (28 days) in each dose-level cohort, and is Grade 3 or higher according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0, with the exceptions as defined below:

For elevations in hepatic function tests, a DLT is defined as follows:

Grade 3 or higher aspartate aminotransferase (AST)/alanine aminotransferase (ALT) levels, OR

[illegible]

Myelosuppression and associated complications are expected events during leukemia therapy, however, the following prolonged myelosuppression is considered a DLT:

Absolute neutrophil count (ANC) <0.5 × 10^9/L, platelets <20 × 10^9/L, and marrow cellularity <5% at 6 weeks or later from start of therapy without any evidence of leukemia.

However, completion of the 28-day safety evaluation is sufficient for the subject to be evaluable. If a DLT based on myelosuppression occurs after the cohort review and dose escalation decisions, dose level assignment of the next subject in the new cohort will be based on an updated BLRM using DLT outcome data from all assessed dose cohorts.

Subjects who are unable to complete at least 75% of the prescribed dose of milademetan or at least 75% of the prescribed

dose of quizartinib in Cycle 1 (28 days) as a result of nondisease-
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The following AEs are not considered DLTs:

Grade 3 fatigue lasting <3 days.

Grade 3 nausea or vomiting that has resolved to Grade 2 within 48 hours following administration of preventive, as well as additional, antiemetic therapies for managing established nausea or vomiting.

Grade 3 diarrhea that has resolved to Grade 2 within 48 hours after standard antidiarrheal therapies.

Alopecia.

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S Δt wκ 1 within 24 hours.

Part 2 (Dose Expansion):

The dose expansion part will begin after the completion of the dose escalation part and will enroll in 2 parallel cohorts of approximately 40 subjects each; dose expansion subjects will be treated at the RDE to confirm safety and tolerability, and to assess the preliminary efficacy of the combination therapy at the RDE. Cohort 1 will enroll subjects with FLT3-ITD mutant AML who were refractory to or had relapsed after prior AML therapy (R/R AML). Cohort 2 will enroll AML therapy-naive subjects with FLT3-ITD mutant AML who are unfit to receive intensive induction chemotherapy.

In a subgroup of the first 12 subjects in Part 2 Cohort 1 (R/R AML), subjects will additionally be dosed with milademetan alone at the RDE dose on Day 1 of Cycle 1 to evaluate the drug-drug interaction (DDI) between milademetan and quizartinib; the rest of the treatment schedule will be identical to the other subjects in Part 2, except that the drugs are administered in unfed conditions in the substudy. Subjects in the DDI substudy are not allowed to receive strong CYP3A inhibitors within 7 days prior to the first dose OR 5 terminal half-lives, whichever is longer. Strong CYP3A inhibitors will only be allowed in the DDI substudy subjects after completion of the first 2 cycles with the recommended dose reductions of milademetan and quizartinib.

Study Duration:	The duration of subject participation is not fixed in this study. Participation in the study begins when the subject signs the informed consent and ends after the 30 (± 5) days follow-up after the last dose of study treatment (30-day Follow-up) followed by

	site visits or phone calls every 3 months (Long-term Survival Follow-up). Subjects who continue to derive clinical benefit from treatment in the absence of withdrawal of subject consent, disease progression, or unacceptable toxicity may continue treatment. When all the subjects enrolled in the study have either completed the Long-term Survival Follow-up, have discontinued, or have completed at least 6 months of treatment, primary analysis will begin. The study is expected to last approximately 4 to 5 years from the time the first subject is enrolled in Part 1 of the study.
Study Sites and Location:	**Dose Escalation**: Approximately 15 sites in the United States, Japan, Asia, and Europe. Additional sites and countries may be added as needed. **Dose Expansion**: Along with the 15 sites for dose escalation, approximately 15 additional sites worldwide may be added as necessary for the dose expansion part, which will commence after the completion of the dose escalation part, based on the enrollment rate, the prevalence of the subject population, and the standard of care available to the subjects at the time.
Subject Eligibility Criteria:	**Inclusion Criteria (Part 1 and Part 2)** 1. Subjects with histological confirmation of primary, secondary, or therapy-related AML according to the 2016 World Health Organization criteria classification with FLT3-ITD mutation 1 =. (R[g=-ITD/total FLT3). Part 1 R/R AML o Subjects who have treatment failure to prior AML therapy (defined as failure to achieve at least CRi) or have relapsed after prior AML therapy, and o f πu–xvηβ(: D(xt Δβ(–'w Part 2 o Cohort 1 R/R AML (same as Part 1) o Cohort 2 Subjects with newly diagnosed AML who are ineligible for intensive induction chemotherapy. Subjects must have had no prior AML treatment, with the exceptions of therapy for antecedent hematologic malignancies (eg, azacitidine for myelodysplastic syndrome) or hydroxyurea. a. f πu–xvηβ(CA(xt Δs old, OR b. Subjects between 18 and 74 years old (inclusive) with at least one of the following comorbidities:

Eastern Cooperative Oncology Group (ECOG) Performance Status of 3;

Cardiac history of congestive heart failure (CHF) requiring treatment, left ventricular ejection fraction (LVEF) A9. 5(−Δ(v≤Δ−„,≥v(stable angina;

Diffusing capacity of the lung for carbon ’ −„,− ≥wx(lP [Ob 2(BA (−Δ(y−Δvxw(x ×≥Δt η−Δ (−”π’ x(≥„(: (βxv−„w(lRQi : 2(BA G

Any other comorbidity that the Investigator judges to be incompatible with intensive chemotherapy must be reviewed by the Sponsor Medical Monitor during screening and before study enrollment.

Note: In both Part 1 and Part 2, subjects with a known record of FLT3-ITD mutant AML within the last 30 days from informed consent based on local testing can enroll in the study. FLT3-ITD status will be tested in a central laboratory for confirmation of eligibility, and any results indicating absence of FLT3-ITD will be communicated to the Investigator for possible discontinuation of the subject from study participation if ongoing clinical benefit is not observed. Subjects in Part 2 who do not show confirmation of FLT3-ITD mutation by central laboratory testing will be replaced. However, those who are deriving clinically benefit may be allowed to continue treatment.

2. Has an ECOG Performance Status:

   In Part 1 and Part 2 Cohort 1 (subjects with R/R AML):

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   In Part 2 Cohort 2 (subjects with newly diagnosed AML):

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   - 0 to 3 for subjects between 18 and 74 years old (inclusive)

3. Has adequate renal function, defined as creatinine clearance 60 mL/min, as calculated using the modified Cockcroft-Gault equation ([{140 age in years} × {actual weight in kg}] divided by [{72 × serum creatinine in mg/dL}] multiply by 0.85 if female), OR if creatinine clearance 50-60 ’ [8’ ≥„(Ma P (≤t β(βxΔπ’ (vΔxt η≥„≥„x(: 7A((π××xΔ(”≥ ≥η(−y(normal (ULN) (in obese subjects, the lean body weight can be used in the equation instead of actual body weight).

4. Has electrolyte levels (including those for potassium, calcium, and magnesium) within normal limits.
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6. Serum total bilirubin : 7A((h [a (1 =((h [a (≥y(wxx' xw(elevated due to leukemia or in subjects with documented S≥'uxΔη β(Syndrome).
7. Discontinuation of prior AML treatment before the start of study treatment (except hydroxyurea to control leukocytosis) for at least 2 weeks for cytotoxic agents, or for at least 5 half-lives for non-cytotoxic agents. Hydroxyurea is allowed until 48 hours prior to start of the study treatment.
8. Subject, if female of childbearing potential, must have a negative serum pregnancy test upon entry into this study and must be willing to use highly effective birth control during the period of therapy and for 6 months following the last investigational drug dose. A female is considered of childbearing potential following menarche and until becoming postmenopausal (no menstrual period for a minimum of 12 months), unless permanently sterile (undergone a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or confirmed by follicle stimulating hormone (FSH) test. If male, must be surgically sterile or be willing to use 1 form of highly effective contraception method upon enrollment, during the course of the study, and for 6 months following the last investigational drug dose.
9. Willingness to abstain from grapefruit/grapefruit juice and Seville oranges from 7 days before the first dose of study drug on Day 1 until the end of the study.
10. Able and willing to provide bone marrow biopsies/aspirates and buccal swab/saliva for PGx testing as requested by the protocol.

Exclusion Criteria

1. Presence of central nervous system (CNS) involvement of leukemia. Patients with a history of CNS leukemia may be eligible if the CNS leukemia is adequately controlled (defined as no active clinical symptoms of CNS disease and at least 2 consecutive lumbar punctures with no evidence of disease prior to study enrollment) after discussion with the Sponsor Medical Monitor.
2. Acute promyelocytic leukemia (AML subtype M3).

3. Has other concurrent malignancy that required systemic antineoplastic treatment within the previous 2 years, except for localized cancers that have apparently been cured (eg, non-melanoma skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast).
4. Uncontrolled or significant cardiovascular disease, including:
   a. QTcF interval >450 ms (average of triplicate determinations).
   b. Bradycardia of less than 50 bpm unless the subject has a pacemaker.
   c. Diagnosed or suspected long QT syndrome, or known family history of long QT syndrome.
   d. History of clinically relevant ventricular arrhythmias, such as ventricular tachycardia, ventricular fibrillation, or torsade de pointes.
   e. History of second or third degree heart block. Subjects 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.
   f. Myocardial infarction within 6 months prior to Screening.
   g. Uncontrolled angina pectoris within 6 months prior to Screening.
   h. New York Heart Association (NYHA) Class III or IV congestive heart failure.
   i. W„− „([i QR(A9. (−Δ(≥„βητηπη≥„„t'('− xΔ('≥ ≥η(−у(„−Δ t''.

      As an exception, subjects with newly diagnosed AML between 18 and 74 years old (inclusive) in Part 2 O−≤−Δη(; (≥η≤([i QR(A9. (−Δ(≥„βητηπη≥„„t'('− xΔ('≥ ≥η(of normal will be eligible.
   j. W„− „(P [Ob (BA (−Δ(RQi : (BA .

      As an exception, subjects with newly diagnosed AML between 18 and 74 years old (inclusive) in Part 2 Cohort 2 with P [Ob (BA (−Δ(RQi : (BA (≥''(ux(eligible.
   k. Uncontrolled hypertension.
   l. Left bundle branch block.
5. Has an uncontrolled infection requiring intravenous antibiotics, antivirals, or antifungals.

6. Has known human immunodeficiency virus infection that is uncontrolled (increasing plasma HIV RNA viral load) with medication, or active hepatitis B or C infection based on positive tests during Screening.
7. Persistent, clinically significant >Grade 1 non-hematologic toxicity from prior AML therapies.
8. Pregnant or breast feeding.
9. Receiving drugs that are strong inducers of CYP3A or v–„βπ’ ×ηϱ–„(–y(f η(V–≤„ β(j –Δ(l≤ ×xΔ≥v≥„2(≥η≤„(: >(wt β(prior to the first dose and during treatment.
10. Received anti-AML therapy (except for hydroxyurea) within the following washout periods before starting study medication:

    Seven days OR 5 half-lives, whichever is longer, for small molecule drugs.

    Twenty-one days OR 5 half-lives, whichever is shorter, for antibody-based, immune-based, biologic, or cellular therapies.
11. Has received allogenic hematopoietic cell transplantation (HCT) within 60 days of the first dose of study drugs.
12. Clinically significant graft versus host disease (GVHD) or GVHD requiring initiation of systemic treatment or systemic treatment escalation within 21 days prior to Screening and/or >Grade 1 persistent or clinically significant GVHD or other non-hematologic toxicity related to HCT.
13. Medical condition, serious intercurrent illness, or other v≥Δvπ’ βη„vx(η≤t ηϱ≥„(η≤x(U„ xβη≥z t η–Δβ(–πwz’ x„,ηϱ(v–π’w(–x–×t Δv≥ x(η≤x(vt „,w≥wt ηx β(βt yxη (as a study subject, or that could interfere with study objectives.
14. Prior treatment with mouse double minute homolog 2 (MDM2) inhibitors.

<u>Additional exclusion criterion for the Part 2 Cohort 1 subgroup of 12 subjects for the DDI substudy</u>

15. Receiving drugs that are strong CYP3A inhibitors within 7 days OR 5 terminal half-lives, whichever is longer, prior to the first dose and until completion of 2 cycles of treatment.

Dosage Form, Dose and Route of Administration:	<u>Quizartinib</u> is a small molecule inhibitor of FLT3. The drug is supplied as tablets in strengths of 20 mg quizartinib hydrochloride

	(17.7 mg free base) and 30 mg quizartinib hydrochloride (26.5 mg free base) for oral administration. Milademetan is a small molecule inhibitor of MDM2-p53 interaction that activates p53 pathway. The drug is supplied as capsules in strengths of 5 mg, 20 mg, 30 mg, 45 mg, 80 mg, 100 mg, and 200 mg for oral administration. The indicated capsule strengths are equivalent to the amount of free base (DS-3032a). Milademetan (DS-3032a) is the free base and the active moiety of the salt form (DS-3032b). The salt form (DS-3032b) is the active pharmaceutical ingredient of the oral capsule formulation. Throughout the remainder of this document, DS-3032a and DS-=9=; u(≥”{ux(ΔxyxΔxw(η–(t β(’ ≥t wx’ xη„ (π„,’xββ(≥„w≥vt ηxw(otherwise. The 2 investigational drugs will be administered in combination as indicated in the dose escalation and dose expansion parts of the study. Quizartinib and milademetan may be administered without regard to the timing of food, except as noted for the DDI substudy.
Study Endpoints:	**Primary Endpoint:** The primary endpoints for safety will include serious adverse events (SAEs), TEAEs, DLTs, physical examination findings (including ECOG Performance Status), vital sign measurements, clinical laboratory parameters (serum chemistry and hematology), and electrocardiogram (ECG) parameters, particularly the QTcF. Adverse events will be categorized using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0. Adverse events and laboratory test results will be graded using the NCI-CTCAE version 5.0. **Secondary Endpoints** The secondary endpoints for PK will include maximum plasma concentration (Cmax) and area under the plasma concentration-time curve up to time 24 hours (AUC24h) for milademetan, quizartinib, and AC886 estimated by non-compartmental analysis, as well as their plasma concentrations at different timepoints relative to dosing. Efficacy endpoints in both Part 1 and Part 2 include the following: CR rate CRi rate CRc rate (CR+CRi)

	DOR: Time from the first objective evidence of CRc to the first objective evidence of relapse or death MLFS rate PR rate ORR (CRc+MLFS+PR) SD rate CRh rate o CRh will be evaluated separately from the other response criteria
Planned Sample Size:	The dose escalation part of this study will be guided by a BLRM for dual agent combination and governed by the EWOC principle. Because of the adaptive nature of the dose escalation part of the trial, the exact sample size is unknown. Based on prior assumptions and simulations, the sample size is expected to have a median of 21 subjects. Approximately 24 to 36 DLT-evaluable subjects are needed to determine the MTDs and RDE. The dose expansion part will commence after the completion of the dose escalation part and will enroll in 2 parallel cohorts of approximately 40 subjects each (total of approximately 80 subjects); dose expansion subjects will be treated at the RDE to confirm the safety and tolerability and to assess the preliminary efficacy of the combination therapy at RDE. Cohort 1 will enroll subjects with FLT3-ITD mutant R/R AML. Cohort 2 will enroll approximately 40 treatment-naive subjects with FLT3-ITD mutant AML who are unfit to receive intensive induction chemotherapy.
Statistical Analyses:	The primary objective of this study is to assess the safety, tolerability of milademetan in combination with quizartinib and establish RDE in subjects with FLT3-ITD mutant AML. Statistical analysis as described below will occur after all subjects from both dose escalation and dose expansion have either completed the study or discontinued from the study or have received at least 6 months of therapy. However, the ongoing subjects deriving clinical benefit may continue to receive the treatment. The primary endpoint of safety (including TEAEs, SAEs, ECGs, etc) will be descriptive and will be presented in tabular format with the appropriate summary statistics. In the dose escalation part, the number of DLTs will be listed for each dose cohort of milademetan in combination with quizartinib.

The secondary endpoint of efficacy will include the rates of CR, CRi, CRc, DOR, MLFS, PR, ORR, SD, and CRh. The efficacy endpoints will be listed and summarized using descriptive statistics. For response rates (CRc, ORR, etc), point estimates and 95% exact binomial confidence intervals will be provided. Time to event endpoint (DOR) will be summarized descriptively using the Kaplan Meier method.

For the secondary endpoint of PK, plasma concentrations of milademetan, quizartinib, and AC886 will be listed and summarized using descriptive statistics by dose cohort at each timepoint. A non-compartmental analysis will be performed to estimate the PK parameters Cmax, time to reach maximum plasma concentration (Tmax), AUC24h, and time to reach maximum plasma concentration (Ctrough) for the 3 analytes.

Drug-drug interaction assessment between milademetan and quizartinib will be performed in a substudy of 12 subjects in Part 2 Cohort 1 by comparing the PK parameters (Cmax and AUC24h). In this substudy, concomitant administration of strong CYP3A inhibitors will be prohibited for the first 2 cycles of treatment. Effects of quizartinib after repeated doses on single dose milademetan PK (Cmax and AUC24h) will be assessed by analysis of variance (ANOVA) model where reference and test treatments for milademetan PK will be Cycle 1/Day : and Cycle 2/Day 1, respectively. The effect of milademetan after repeated doses on steady-state quizartinib and AC886 PK (Cmax and AUC24h) will also be evaluated using an ANOVA model where the reference and test treatments for quizartinib and AC886 PK will be Cycle 1/ Day 28 and Cycle 2/Day 14, respectively. The PK parameters will be transformed prior to analysis using a natural logarithm-transformation. The 90% confidence intervals for the ratios of the geometric means for the PK parameters (Cmax and AUC24h) will be calculated.

Lastly an exposure-response analysis may also be performed to assess the relationship between plasma exposure of milademetan, quizartinib and AC886 and ECG, particularly QTcF. The population PK and efficacy response analyses may be reported separately from the clinical study report.

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ABBREVIATION	DEFINITION
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC24h	Area Under the Plasma Concentration-time Curve up to Time 24 Hours
AUCinf	Area Under the Plasma Concentration-time Curve up to Infinity
BLRM	Bayesian Logistic Regression Model
Cmax	Maximum Plasma Concentration
CR	Complete Remission
CRc	Composite Complete Remission
CRh	Complete Remission with Partial Hematological Recovery
CRi	Complete Remission with Incomplete Blood Count Recovery
CRF	Case Report Form
CRO	Contract Research Organization
Ctrough	Trough Plasma Concentration
DDI	Drug-drug Interaction
DISS	Drug-≥,wπvxw(f xxηβ(f „wΔ–’ x
DLCO	Diffusing Capacity of the Lung for Carbon Monoxide
DLT	Dose Limiting Toxicity
DOR	Duration of Composite Complete Remission
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EFS	Event-free Survival
EIU	Exposure In Utero
ELN	European LeukemiaNet

ABBREVIATION	DEFINITION
EWOC	Escalation with Overdose Control
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 Second
FLT3	FMS-like Tyrosine Kinase 3
FLT3-ITD	FMS-like Tyrosine Kinase 3 Internal Tandem Duplication
GCP	Good Clinical Practice
GI	Gastrointestinal
GVHD	Graft Versus Host Disease
Hgb	Hemoglobin
HCT	Hematopoietic Cell Transplant
IB	Investigator s Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
ITD	Internal Tandem Duplication
IXRS	Interactive Web/Voice Response System
LSC	Leukemic Stem Cells
LVEF	Left Ventricular Ejection Fraction
MDM2	Mouse Double Minute 2 Homolog
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
MLFS	Morphologic Leukemia-free State
MRD	Minimal Residual Disease
MUGA	Multigated Acquisition
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
ORR	Overall Response Rate
OS	Overall Survival
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PGx	Pharmacogenomics

ABBREVIATION	DEFINITION
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PR	Partial Remission
qd	Once Daily
QTcF	QTc by Friw⁄Δ≥v≥t β(’ xη≤−w
RDE	Recommended Dose for Expansion
R/R	Relapsed/Refractory
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent Adverse Event
Tmax	Time to Reach Maximum Plasma Concentration
TR	Transplantation Rate
ULN	Upper Limit of Normal
US	United States

1. INTRODUCTION

1.1. Background

FMS-like tyrosine kinase 3 (FLT3) is expressed in hematopoietic progenitor cells, and signaling through FLT3 promotes proliferation and survival in these cells. FLT3 internal tandem duplication (FLT3-ITD) occurs in approximately 25% of subjects with acute myeloid leukemia (AML).[1,2] The FLT3-ITD mutation is associated with a shorter duration of response, a greater cumulative incidence of relapse, and shorter survival after relapse. There is an unmet medical need for effective treatment for patients with relapsed/refractory (R/R) AML with the FLT3-ITD mutation. In FLT3-ITD mutant AML, constitutive FLT3 signaling results in activation of STAT5 leading to transcriptional upregulation of Mcl-1, Bcl2, c-Myc, and other proteins that support survival and proliferation of the leukemic cells and survival of the leukemic stem cells (LSCs).[3,4,5] Duration of response is still short with the currently studied FLT3 inhibitors, and an effective therapy for durable responses in FLT3-ITD mutant AML should target the FLT3 signaling and survival mechanisms of the LSC.

Quizartinib (AC220) is a potent and selective inhibitor of FLT3 that is currently in Phase 3 trials, and previous Phase 1 and Phase 2 studies of quizartinib monotherapy have shown high response rates in patients with R/R FLT3-ITD mutant AML.

A Phase 2 study of quizartinib monotherapy (2689-CL-2004) randomized 76 subjects with FLT3-ITD mutant AML who were refractory to or had relapsed after second-line AML therapy with or without consolidating hematopoietic cell transplant (HCT) to a starting dose of 30 mg or 60 mg once daily (qd) with intra-subject dose escalation allowed to 60 mg or 90 mg daily, respectively, after 1 cycle. The rates of composite complete remission (CRc) through the End-of-treatment were the same (47%) in both groups and were consistent with the rate observed at higher doses (90 mg, 135 mg, and 200 mg daily) in subjects with R/R FLT3-ITD mutant AML in an earlier Phase 2 study (49%). In the 30 mg and 60 mg dose groups, the dose was escalated in 63% and 19% of subjects, respectively. The duration of CRc was 4.2 and 9.1 weeks, and median overall survival was 20.9 and 27.3 weeks in the 30 mg and 60 mg dose groups, respectively.

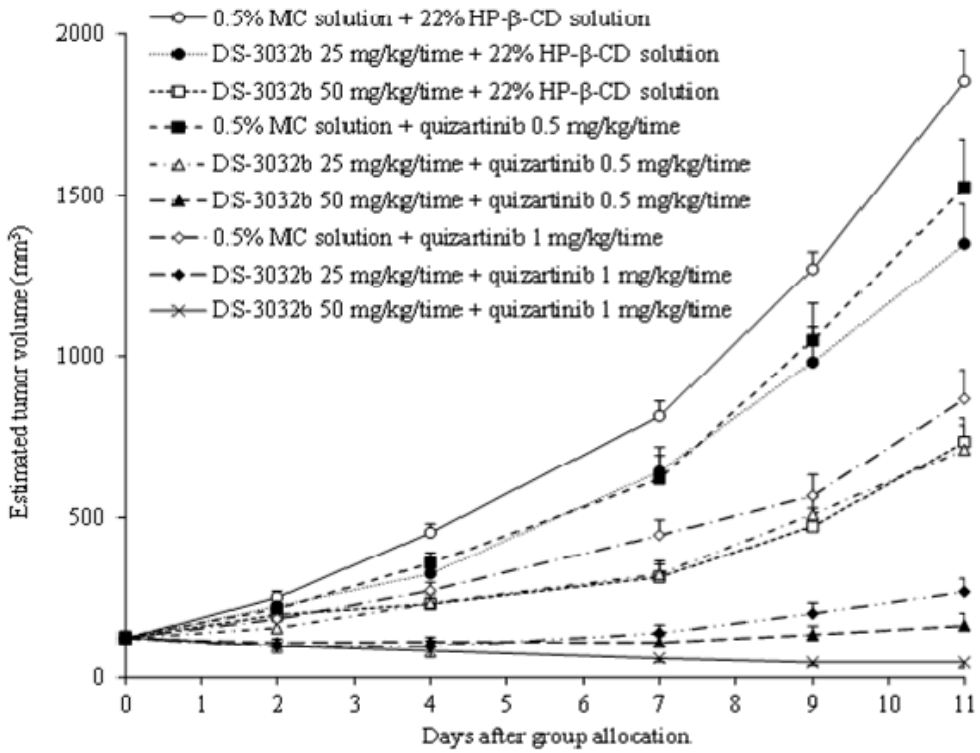
The tumor suppressor protein p53 (encoded by TP53 gene) plays an essential role in preventing neoplasia by inducing cell cycle arrest or apoptosis in cells undergoing various types of physiological stress. Inactivation of TP53 by mutation occurs in approximately half of human tumors, resulting in loss of tumor suppressor activity, and thereby removing a pivotal barrier to neoplastic development. More than 90% of AML patients retain wild type TP53 in the malignant cells, but the p53 protein activity is frequently inhibited by binding of overexpressed mouse double minute 2 homolog (MDM2) in these cells, resulting in ubiquitination and proteasomal degradation of p53.[6] Pharmacologic inhibition of the interaction between MDM2 and wild type p53 in tumor cells could restore p53 activity with subsequent antitumor effects from the p53-downstream genes.[7]

DS-3032b (International Nonproprietary Name: milademetan), a novel, specific, small molecule inhibitor of MDM2, disrupts interactions between MDM2 and the tumor suppressor protein p53 in tumor cells, and is currently being developed as an oral drug for the treatment of solid tumors and hematological malignancies. MDM2 inhibition and antileukemic effect were demonstrated in a Phase 1 open-label study (DS3032-A-U102) in subjects with advanced hematological

malignancies. As of 08 Jan 2018, the dose escalation part has enrolled and treated 52 subjects with AML or high risk myelodysplastic syndrome (MDS). Thirty-seven subjects were treated at a dosing schedule of qd for 21 out of a 28 days cycle (qd 21/28) at doses starting from 60 mg and then at increasing doses of 90 mg, 120 mg, 160 mg, and 210 mg. Maximum tolerated dose (MTD) was determined to be 160 mg in the qd 21/28 schedule. An additional 15 subjects were treated under alternative, dosing schedules currently under investigation (7 subjects at 160 mg qd 7/28, 3 subjects at 160 mg 3/14 twice in a 28 day cycle, 4 subjects at 160 mg qd 14/28, and 1 subject at 220 mg qd 14/28). Ten of the 15 subjects treated in the alternative dosing schedules were evaluable for dose limiting toxicities (DLTs), and no DLTs have been observed in these subjects. The remaining 5 subjects were not evaluable due to discontinuation before completing the Cycle 1 evaluation. Among the subjects treated under the qd 21/28 dosing schedule, bone marrow blast reduction was noted in 14/26 (54%) evaluable subjects with at least 1 post-dose assessment. Q≥z≤η(βπu–xvηβ(t v≤x xw(50% blast reduction and 2 subjects achieved complete remission (CR). Three additional subjects achieved blast reduction to <5% without peripheral blood count recovery that correspond to morphologic leukemia-free state. Best response in all subjects was achieved after the first cycle of therapy.

To evaluate the potential benefit of combining a FLT3 inhibitor and MDM2 inhibitor for the treatment of patients with FLT3-ITD mutant AML, an in vivo nonclinical pharmacology study was conducted in male NOD SCID mice bearing MOLM-13 (FLT3-ITD mutant; p53 wild type) human AML xenografts by treatment with both milademetan and quizartinib orally qd for 11 days after establishing the tumors (Figure 1.1).

Figure 1.1: Effects of Milademetan and Quizartinib on Estimated Tumor Volume in MOLM-13-bearing NOD SCID Mice



Quizartinib was dosed daily at 0.5 mg/kg and 1 mg/kg and milademetan was dosed daily at 25 mg/kg and 50 mg/kg. Antitumor effects were assessed based on estimated tumor volume on Day 11. In all cases, synergistic activity was seen for all doses of the 2 drugs in combined treatment, showing superior tumor inhibition by these combinations compared to either agent alone. The synergistic effect between quizartinib and milademetan was also observed in other preliminary experiments using AML FLT3-ITD mutant/TP53WT cell lines.

Quizartinib is a substrate for CYP3A and P-glycoprotein (P-gp). The clinical data suggest that P-gp plays a minimal role in the absorption or clearance of quizartinib. Therefore, no dose adjustment is required when quizartinib is co-administered with a P-gp inhibitor or a P-gp inducer. However, a dose adjustment for quizartinib is required if administered concomitantly with a strong CYP3A inhibitor, but not with moderate or weak inhibitors of CYP3A. Quizartinib is neither an inhibitor nor an inducer of CYP3A, and is thus unlikely to inhibit milademetan metabolism. Quizartinib may have the potential to inhibit P-gp in vivo.

Milademetan is a substrate for CYP3A and P-gp. A Phase I study in healthy subjects was conducted to evaluate the effect of co-administration of strong CYP3A inhibitors (itraconazole and posaconazole) on milademetan PK (DS3032-A-U107). Co-administration of milademetan 100 mg with itraconazole 200 mg at steady state increased milademetan mean maximum plasma concentration (Cmax) and area under the plasma concentration-time curve up to infinity (AUCinf) by 8% and 115%, respectively. Similarly, posaconazole 200 mg at steady state increased milademetan mean Cmax by approximately 19% and AUCinf by approximately 149%. Therefore, it is recommended that the milademetan dose be reduced by half when it is concomitantly administered with a strong CYP3A inhibitor.

Milademetan is likely a moderate or weak inhibitor of both CYP3A and P-gp. Milademetan is expected to result in minimal change in quizartinib pharmacokinetics (PK) based on the in vitro and in vivo assessment of drug-drug interaction (DDI) potential. However, the in vivo DDI potential between quizartinib and milademetan through P-gp inhibition needs to be evaluated in a clinical study.

1.2. Study Rationale

Combined treatment of quizartinib and milademetan has the potential to show synergistic antileukemic activity by targeting 2 distinct cellular pathways: FLT3-ITD signaling pathway and p53 activation pathway. Quizartinib suppresses the induction of Bcl2 family survival proteins (Mcl-1, Bcl2) by inhibiting FLT3-ITD signaling and preventing STAT5 activation. MDM2 inhibition increases p53 levels and the p53-induced proteins (eg, PUMA and NOXA) that inactivate the anti-apoptotic Bcl2 family proteins by direct binding, thereby suppressing the anti-apoptotic mechanisms in the FLT3-ITD mutant AML and LSCs.[8,9] While several cytotoxic agents can also induce p53 in proliferating cells, MDM2 inhibitors will increase p53 levels irrespective of cell proliferation in the relatively quiescent LSCs. Each of these treatments also exerts other antileukemic effects contributing to their overall synergy. FLT3-ITD constitutive signaling leads to the induction of oncogenic proteins (eg, c-MYC and pim-2) that will be suppressed by quizartinib,[10] while increased levels of p53 resulting from MDM2 inhibition also induces pro-apoptotic Bcl2 family proteins including BAX.[11] In addition, p53 activation has been reported to block the stroma cell-mediated resistance to FLT3 inhibition by downregulating the production of CXCL12 by bone marrow stromal cells.[12] Therefore, a combination of these 2

agents aimed at inhibiting FLT3 and re-activating p53 function by MDM2 inhibition could potentially be effective in FLT3-ITD mutant AML by a stronger induction of the mitochondrial initiated apoptosis on the bone marrow blasts and the LSCs, and by suppressing the stromal cell-mediated survival signals.

The scientific rationale and the nonclinical and available clinical data support the clinical investigation of the combined treatment of quizartinib and milademetan in subjects with FLT3-ITD mutant AML.

1.3. Potential Risks for Study Subjects

DS3032-A-U105 is a first-in-human co-development study of 2 investigational agents: milademetan and quizartinib. The safety, tolerability, and PK of quizartinib have been extensively evaluated in humans. Adverse reactions with quizartinib from studies to date include general disorders (eg, pyrexia and fatigue), gastrointestinal disorders (eg, nausea, diarrhea, and vomiting), hematologic disorders (eg, anemia, neutropenia, and thrombocytopenia), QTc prolongation, torsades de pointes, neutrophilic dermatosis/differentiation syndrome, DDIs with strong CYP3A inhibitors, DDIs with strong or moderate CYP3A inducers, and the consequences of cytopenias including increased risk of infection and bleeding.

Based on early clinical studies that have been conducted with milademetan, the adverse events (AEs) anticipated with milademetan are primarily related to the gastrointestinal tract (eg, nausea, vomiting, diarrhea, and poor appetite), marrow suppression (primarily thrombocytopenia), electrolyte disturbances, and DDIs with strong CYP3A inhibitors.

For the combination studies of quizartinib with milademetan, while there is some overlap between the AE profiles of the 2 drugs (especially with respect to myelosuppression, infection, and gastrointestinal AEs) and the background disease pathology, all of these events can be monitored and are manageable. Investigators specializing in treating AML subjects are very familiar with the identification and management of these types of AEs and the protocol is designed to facilitate their detection. Milademetan does not bind human ether-a-go-go-related gene (hERG) channels and had no effects in dog telemetry studies, making it unlikely that combining milademetan with quizartinib would affect quizartinib-associated alterations in QT interval.

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Study Objectives

2.1.1. Primary Objectives

Part 1 (Dose Escalation):

To determine the safety and tolerability of the drug combination, identification of the optimum dosing schedule, MTD, and the recommended dose for expansion cohort (RDE).

Part 2 (Dose Expansion):

To confirm safety and tolerability of the combination therapy at RDE and to identify the recommended Phase 2 dose.

Assessment of efficacy.

2.1.2. Secondary Objectives

Part 1 only:

Preliminary assessment of efficacy.

Part 1 and Part 2:

To evaluate the PK of milademetan, quizartinib, and the active metabolite of quizartinib, AC886.

2.1.3. Exploratory Objectives

Part 1 and Part 2:

To evaluate the pharmacodynamic effects of the combination treatment at each dose level.

Part 2 only:

Additional assessments of efficacy.

2.2. Outcome Measures

2.2.1. Primary Outcome Measures

Part 1 only:

- Number of subjects with DLTs.

[Time Frame: Approximately 18 months from start of the study]

Part 1 and Part 2:

Number of subjects who experienced an AE during the study.

[Time Frame: Approximately 3 years from start of study]

Part 2 only:

Number of subjects with response to treatment.

Response to treatment will be assessed using 2017 European LeukemiaNet (ELN) recommendations. These include the rates of CR; CR with incomplete blood count recovery (CRi); CRc; duration of composite complete remission (DOR); morphologic leukemia-free state (MLFS); partial remission (PR); overall response rate (ORR); and stable disease (SD). CR with partial hematological recovery (CRh) will be evaluated separately from the other response criteria.

[Time Frame: Approximately 3 years from start of study]

2.2.2. Secondary Outcome Measures

Part 1 only:

Number of subjects with response to treatment.

Response to treatment will be assessed using 2017 ELN recommendations. These include the rates of CR, CRi, CRc, DOR, MLFS, PR, ORR, and SD. CRh will be evaluated separately from the other response criteria. The efficacy measurements are listed in Section 2.4.3.

[Time Frame: Approximately 18 months from start of study]

Part 1 and Part 2:

Plasma concentrations and PK parameters of milademetan, quizartinib, and AC886.

[Time Frame: Approximately 3 years from start of study]

2.2.3. Exploratory Outcome Measures

Part 1 and Part 2:

Pharmacodynamic and biomarker measurements.

Part 2 only:

Additional measurements to assess number of subjects with response to treatment.

2.3. Study Hypothesis

Combined treatment of subjects with FLT3-ITD mutant AML with quizartinib and milademetan will be safe and well tolerated and will show enhanced anti-leukemic activity over that observed in the previous single agent studies.

2.4. Study Endpoints

2.4.1. Safety Endpoint

The primary safety endpoints will include serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), DLTs, physical examination findings (including Eastern Cooperative Oncology Group [ECOG] Performance Status), vital sign measurements, clinical laboratory parameters (serum chemistry and hematology), and electrocardiogram (ECG) parameters, particularly the QTc by Friw×Δ≥≥t β(’ xη≤−w(ld g vR2. Adverse events (AEs) will be categorized using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0. Adverse events

and laboratory test results will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

2.4.2. Pharmacokinetic/Pharmacodynamic/Biomarker Endpoint(s)

Pharmacokinetics

Plasma concentrations relative to dosing for milademetan, quizartinib, and AC886.

PK parameters (Cmax and area under the plasma concentration-time curve up to time 24 hours [AUC24h]) for milademetan, quizartinib, and AC886 estimated by non-compartmental analysis.

Effect of quizartinib on milademetan PK and effect of milademetan on quizartinib PK in the DDI substudy in the dose expansion part.

Pharmacodynamics

Pharmacodynamic assessments are exploratory endpoints and may include, but are not limited to, the following:

Changes in LSC numbers.

Changes in FLT3 signaled STAT5 downstream gene expression (eg, Mcl-1, Bcl2, c-Myc), and p53 downstream targets (eg, MDM2, MIC-1, PUMA, NOXA, Bax, CXCL12) in bone marrow AML or peripheral blood blasts and/or non-leukemic cells.

Changes in circulating proteins such as MIC-1 and/or cell surface or cellular proteins.

Minimal residual disease (MRD) may be tested in the bone marrow or peripheral blood samples obtained from subjects who achieve a reduction of blasts in bone marrow to <5%.

Baseline and post-baseline mutation status of genes involved in AML pathogenesis.

Other biomarkers

FLT3-ITD status of the leukemic cells will be tested in a central laboratory.

Prior confirmation of TP53 wild type status is not required for starting treatment, but TP53 mutant or wild type status will be retrospectively tested at the end of the study.

2.4.3. Efficacy Endpoint(s)

The secondary endpoints of efficacy include the following assessments. The response rate will be summarized based on the Investigator-assessed best response after the first dose of study treatment and before the last disease assessment during the study (Section 7.1). The response criteria are according to the 2017 ELN recommendations in Section 17.4 and Section 17.5:

CR rate

CRi rate

CRc rate (CR+CRi)

DOR: Time from the first objective evidence of CRc to the first objective evidence of relapse or death

MLFS rate

PR rate

ORR (CRc+MLFS+PR)

SD rate

CRh rate

- CRh will be evaluated separately from the other response criteria

2.4.3.1. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints may include the following assessments:

Transplantation rate: Percent of subjects undergoing allogeneic HCT directly following protocol-specified treatment with no intervening AML therapy

Event-free survival (EFS): Time from first dose date until relapse after CR or CRi, refractory disease, or death from any cause, whichever is observed first

Overall survival (OS): Time from first dose date until death from any cause

Transfusion independence

2.4.4. Other Endpoints

Not applicable.

3. STUDY DESIGN

3.1. Overall Design

This will be an open-label, Phase 1 study of milademetan in combination with quizartinib in subjects with FLT3-ITD mutant AML, with a dose escalation part (Part 1) and a dose expansion part (Part 2). Quizartinib will be administered qd in 28-day cycles, and milademetan will be administered qd on Days 1 to 14 of each 28-day cycle (qd 14/28 schedule) or in alternative dosing schedules.

The dose escalation part of the study is planned to be conducted in approximately 15 sites in the United States (US), Japan, Asia, and Europe. Additional sites and countries may be added as needed.

Along with the 15 sites for dose escalation, approximately 15 additional sites worldwide may be added as necessary for the dose expansion part, which will commence after the completion of the dose escalation part, based on the enrollment rate, the prevalence of the subject population, and the standard of care available to the subjects at the time. The duration of subject participation is not fixed in this study. The study is expected to last approximately 4 to 5 years from the time the first subject is enrolled in Part 1 of the study.

An overview of the study design is provided in Table 3.1.

Table 3.1: Study Design

Part	Cohort	Target Disease	Target Population	Estimated Enrollment (n)
Part 1 *Dose Escalation*	Multiple escalating dosage/schedule cohorts	Relapsed/Refractory AML	f πu–xvrβ(: D(xt Δβ(–'w	Approximately 24 to 36
Part 2 *Dose Expansion*	Cohort 1[a]	Relapsed/Refractory AML	f πu–xvrβ(: D(xt Δβ(–'w	Approximately 40
	Cohort 2	Newly diagnosed AML	Subjects unfit for intensive chemotherapy who are: 75 years old, OR Between 18 and 74 years old with at least 1 comorbidity	Approximately 40

AML = acute myeloid leukemia

[a] The first 12 subjects in Part 2 Cohort 1 will be enrolled as a drug-drug interaction (DDI) substudy cohort to evaluate the DDI between milademetan and quizartinib.

3.1.1. Dose Limiting Toxicity Definition

A DLT is defined as any non-hematological TEAE unless incontrovertibly related to disease progression, intercurrent illness, or concomitant medication, that occurs during the DLT evaluation period (28 days) in each dose-level cohort, and is Grade 3 or higher according to the NCI-CTCAE version 5.0, with the exceptions as defined below:

For elevations in hepatic function tests, a DLT is defined as follows:

> Grade 3 or higher aspartate aminotransferase (AST)/alanine aminotransferase (ALT) levels, OR
>
> Elevation in total bilirubin =.0 × ULN that does not return to Grade 2 elevation within 7 days.

Myelosuppression and associated complications are expected events during leukemia therapy, however, the following prolonged myelosuppression is considered a DLT:

> ANC <0.5 × 10^9/L, platelets <20 × 10^9/L, and marrow cellularity <5% at 6 weeks or later from start of therapy without any evidence of leukemia.

However, completion of the 28-day safety evaluation is sufficient for the subject to be evaluable. If a DLT based on myelosuppression occurs after the cohort review and dose escalation decisions, dose level assignment of the next subject in the new cohort will be based on an updated Bayesian logistic regression model (BLRM) using DLT outcome data from all assessed dose cohorts.

Subjects who are unable to complete at least 75% of the prescribed dose of milademetan or at least 75% of the prescribed dose of quizartinib in Cycle 1 (28 days) as a result of nondisease-Δx'tηκw(S Δtwx(2 events will be considered to have a DLT.

The following AEs are not considered DLTs:

> Grade 3 fatigue lasting <3 days.
>
> Grade 3 nausea or vomiting that has resolved to Grade 2 within 48 hours following administration of preventive, as well as additional, antiemetic therapies for managing established nausea or vomiting.
>
> Grade 3 diarrhea that has resolved to Grade 2 within 48 hours after standard antidiarrheal therapies.
>
> Alopecia.
>
> S Δtwx(=(x'xvηΔ–" ηκ(tu,,–Δ' t'≥ηx≥β(η≤tη(tΔx(v–ΔΔxvηκw(η–(S Δtwx 1 within 24 hours.

3.1.2. Part 1 (Dose Escalation)

Dose escalation will assess the safety, tolerability, PK, and preliminary efficacy of increasing doses of milademetan and quizartinib in subjects with FLT3-ITD mutant R/R AML. The evaluation period for DLTs will be 28 days (Cycle 1) from the start of study drug administration. The dose escalation will be guided by a BLRM for dual agent combination and governed by the escalation with overdose control (EWOC) principle[13,14] (Section 11.12). The determination of MTD(s) will be guided by the BLRM using accumulated DLT data as well as other safety and PK data. The RDE will be decided based on considerations of the respective MTD(s) guided by the BLRM and on an overall assessment of safety data from all cycles, PK data, and preliminary efficacy data.

Cohorts of 3 to 6 subjects will be enrolled and assessed for DLT before escalation to a new higher dose. For a subject to be considered evaluable for DLT, the subject must have received at least 75% of the prescribed Cycle 1 doses and completed safety assessments of the DLT

evaluation period, or experienced a DLT in this period. Subjects who started treatment but who do not meet the criteria to be DLT-evaluable will not be included in the BLRM update. In some cases, a subject in the previous cohort may experience a DLT after the enrollment of subjects to a new cohort has begun. In this event, the dose level assignment of the next subject(s) in the new cohort will be based on an updated BLRM using DLT outcome data from all assessed dose cohorts up to that point.

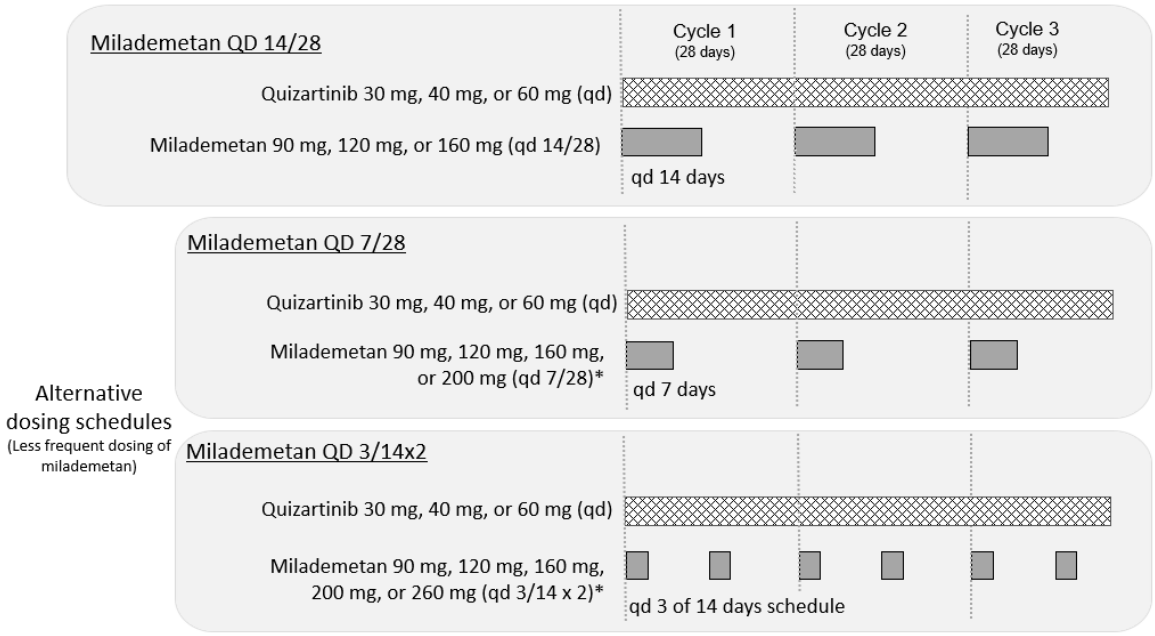
A delay of at least 7 days will occur between the first subject dosed and the second subject dosed in the first cohort. If 2 evaluable subjects in any cohort experience DLT before the enrollment of the next subject, the model will be re-evaluated and discussion between the Investigators and Sponsor will occur before enrollment of any additional subjects in the cohort.

Enrollment of subjects to a new cohort requires completion of DLT evaluation of at least 3 subjects treated in the current cohort at the intended dose levels. The Investigator and Sponsor will also assess safety and tolerability on an ongoing basis and will continue dosing if there are no safety or risk/benefit concerns and if the subject is deriving clinical benefit. Additional subjects for the characterization of safety, PK, or PD may be added at any dose escalation cohort below the MTD dose level or at the MTD in parallel with ongoing escalation up to a maximum of 12 subjects in each cohort. Further details can be found in the Cohort Management Plan.

Milademetan Dose Levels

The proposed starting dose of milademetan will be 90 mg, which will be escalated through 120 mg and 160 mg; all 3 doses will follow the qd 14/28 dosing schedule unless the safety data suggest the use of a less frequent dose schedule. Based on emerging safety and efficacy data during dose escalation, the dose levels of milademetan may be evaluated up to 200 mg or 260 mg in alternative dosing schedules with less frequent doses (eg, Days 1 to 7 of each 28-day cycle [qd 7/28] and Days 1 to 3 of each 14 days administered twice in a 28-day cycle [qd 3/14 × 2]) (Figure 3.1). The maximum dose for milademetan will be up to 260 mg in the qd 3/14 × 2 schedule as determined in the DS3032-A-U101 study.

Figure 3.1: Proposed Dosing Schedule of Quizartinib – Milademetan Combination



* The proposed doses under these schedules include all the possible doses including those previously planned to be evaluated in a more frequent dose schedule but switched to the less frequent schedule based on emerging safety data.

As a conservative approach, the starting dose of milademetan will be 90 mg in a qd 14/28 schedule. This dose is 2 dose levels below the single agent MTD (ie, 160 mg) for AML/MDS in the DS3032-A-U102 study, and 1 dose level below the single agent MTD (ie, 120 mg) for solid tumors in the DS3032-A-U101 study, both following the qd 21 of 28-day schedule (qd 21/28). The maximum dose for milademetan will be up to 260 mg in the qd 3/14 × 2 schedule as determined in the DS3032-A-U101 study.[15]

Quizartinib Dose Levels

There are 3 proposed dose levels of quizartinib: 30 mg, 40 mg, and 60 mg. Quizartinib monotherapy from 30 mg to 60 mg doses was demonstrated to be safe and clinically active in the Phase 2 (2689-CL-2004) study. However, the optimal dose/schedule of quizartinib is unknown when it is combined with milademetan. Therefore, 30 mg qd quizartinib will be used as the starting dose, as this dose demonstrated a similar CRc rate as 60 mg qd quizartinib.[16]

If quizartinib is increased to the 60-mg dose level, subjects will be dosed at 30 mg for the first 14 days to evaluate the QT prolongation risk in each subject. Iy(ηŁx(d g v(u (RΔ≥wxΔ≥v≥t β(’ xηŁ–w(ld g vR2(Δx’ t≥,β(>A9 ms, the dose will be escalated to the intended dose of the cohort (ie, 60 mg quizartinib) on Day 15 of Cycle 1 and continued at the same dose in subsequent cycles. If the QTcF is >450 ms but 480 ms, the subject can continue at 30 mg quizartinib in combination with the assigned dose of milademetan, in the absence of other risk factors. If the QTcF is >480 ms but 500 ms, the subject can continue with a quizartinib dose reduction of 1 level in combination with the assigned dose of milademetan, in the absence of other risk factors. Multiple stepwise dose reductions from 60 mg to 40 mg, 40 mg to 30 mg, and 30 mg to 20 mg are allowed to mitigate the QTcF prolongation risks of the subjects. If the QTcF is >500 ms and recurs despite

appropriate dose reductions and correction/elimination of other risk factors (eg, serum electrolyte abnormalities, concomitant QT-prolonging medication), the subject will be permanently discontinued from quizartinib.

In cohorts with quizartinib 60 mg, it is possible that not all subjects may be assignable to quizartinib 60 mg on Day 15 after the 30 mg lead-in for the first 14 days, and therefore additional subjects may be enrolled for evaluation of the cohorts.

Dose Escalation Plan

The proposed dose levels shown in Table 3.2 were chosen based on the safety and preliminary efficacy data from the single agent studies. The dose and schedule of milademetan will be first optimized during dose escalation in combination with 30 mg qd quizartinib. When a decision is made to escalate the dose, the milademetan dose can be escalated to the next dose level at the existing dosing schedule suggested by BLRM (eg, qd 14/28), at a less frequent dosing schedule (ie, qd 7/28 or qd 3/14 × 2), or in separate cohorts of 2 schedules in parallel; the MTD(s) in those schedules may be separately assessed. While the BLRM will provide the dose recommendation, the decision to use a less frequent dose schedule will be taken after discussion between the Investigators and Sponsor based on the overall safety data thus far. However, dose escalation from any dose level in a less frequent dose schedule to a more frequent dose schedule is not allowed.

Once the most optimal dose and schedule of milademetan is identified, the quizartinib qd dose will be escalated from 30 mg to 40 mg, and then from 40 mg to 60 mg, in combination with the optimal dose of milademetan. During dose escalation, simultaneous dose escalation of both agents will not be not allowed. Additional dose combinations not shown in the table may be tested based on emerging safety data during dose escalation.

Table 3.2: Proposed Cohorts and Dose Levels of Quizartinib and Milademetan for Dose Escalation

Quizartinib Dose	Milademetan Dose
30 mg qd	90 mg qd 14/28[a]
30 mg qd	120 mg qd 14/28[a]
30 mg qd	160 mg qd 14/28[a]
30 mg qd	200 mg qd 7/28[a]
30 mg qd	260 mg qd 3/14 × 2
40 mg qd	Most optimal dose and schedule identified in combination with 30 mg qd quizartinib
60 mg qd following 30-mg lead-in (14 days)	Most optimal dose and schedule identified in combination with 30 mg qd quizartinib

qd = once daily

[a] At any milademetan dose level, if the evaluated dosing schedule is not tolerated, alternative dosing schedules of less frequent doses (eg, qd 7/28 or qd 3/14 × 2) may be evaluated. However, dose escalation from any dose level in a less frequent dose schedule to a more frequent dose schedule is not allowed.

Note: Some of the cohorts shown in the table may be dropped based on the emerging safety data during dose escalation.

3.1.2.1. Stopping Rules (Dose Escalation)

The following stopping rule will be implemented for the dose escalation part:

> At least 6 evaluable subjects have been enrolled at the MTD level with at least 21 evaluable subjects in total enrolled in the dose escalation part.

The RDE will be decided based on considerations of the respective MTD(s) guided by the BLRM and on an overall assessment of safety data from all cycles, PK data, and preliminary efficacy data.

3.1.2.2. Dose Modification of Milademetan due to Thrombocytopenia and/or Neutropenia (Cycle 2 and Later)

If a subject experiences prolonged thrombocytopenia (platelets <50 × 10^9/L) and/or neutropenia (ANC <0.5 × 10^9/L) that is drug-related ≥„(η≤x(U‚ xβ≈zt η¬Δβ(v'≥„≥vt'(¬πwzx' x„,ηbefore starting the subsequent milademetan cycle, then the Investigator after consultation with the Sponsor Medical Monitor may reduce the dose frequency of milademetan (eg, 10/28 days, 7/28 days, or 3/14 days × 2) in subsequent cycles while maintaining the same daily dose of milademetan. Efforts will be made to preferentially adjust the milademetan dose frequency while maintaining quizartinib at a stable dose without interruption for as long as possible.

3.1.3. Part 2 (Dose Expansion)

The dose expansion part will commence after the completion of the dose escalation part and will enroll in 2 parallel cohorts of approximately 40 subjects each (total of approximately 80 subjects); dose expansion subjects will be treated at the RDE to confirm safety and tolerability, and to assess the preliminary efficacy of the combination therapy at the RDE. Cohort 1 will enroll subjects with FLT3-ITD mutant AML who were refractory to or had relapsed after prior AML therapy (R/R AML). Cohort 2 will enroll AML therapy-naive subjects with FLT3-ITD mutant AML who are unfit to receive intensive induction chemotherapy (see eligibility criteria in Section 4.1).

In a subgroup of the first 12 subjects in Part 2 Cohort 1 (R/R AML), subjects will additionally be dosed with milademetan alone at the RDE dose on Day 1 of Cycle 1 to evaluate the DDI between milademetan and quizartinib; the rest of the treatment schedule will be identical to the other subjects in Part 2, except that the drugs are administered in unfed conditions in the substudy (Section 5.2.4). Subjects in the DDI substudy are not allowed to receive strong CYP3A inhibitors within 7 days prior to the first dose OR 5 terminal half-lives, whichever is longer. Strong CYP3A inhibitors will be allowed in the DDI substudy subjects only after completion of the first 2 cycles with the recommended dose reductions of milademetan and quizartinib (Section 3.1.2).

For Part 2 of the study, the Simon 2-stage optimal design will be utilized. In stage 1, a futility analysis will be conducted when Investigator-assessed best response from the first 2 cycles of study treatment are available in 19 evaluable subjects (Section 11.10).

Additionally, after 19 subjects are enrolled in each cohort, if the cumulative incidence of clinically relevant AEs that meet the definition of DLT exceeds 30%, further enrollment in that cohort will be discontinued at the current RDE and a lower dose of milademetan and/or quizartinib will be considered as RDE for re-evaluating the safety of the cohort.

3.2. Discussion of Study Design

This will be an open-label, Phase 1 study of milademetan in combination with quizartinib in subjects with FLT3-ITD mutant AML with a dose escalation part followed by dose expansion. The proposed dose levels for dose escalation in Table 3.2 were chosen based on the safety and preliminary efficacy data in the single agent studies described in Section 1.1. Quizartinib is expected to be the primary mediator of efficacy in this population of FLT3-ITD mutant AML patients with constitutive activation of STAT5 and upregulation of STAT5 target genes including the anti-apoptotic Mcl-1 as a predominant survival factor for the leukemic blasts and LSCs. Therefore, the 30 mg and 60 mg doses of quizartinib that were demonstrated to be safe and clinically active in the Phase 2 (2689-CL-2004) study were chosen, along with an intermediate dose of 40 mg, for the combination with milademetan. Milademetan in combination with any of the above doses of quizartinib in escalating doses from 90 mg may achieve maximal suppression of anti-apoptotic mechanisms by induction of p53 downstream genes.

4. STUDY POPULATION

4.1. Inclusion Criteria

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

1. Subjects with histological confirmation of primary, secondary, or therapy-related AML according to the 2016 World Health Organization criteria classification[17] with FLT3-ITD mutation (3% FLT3-ITD/total FLT3).

   Part 1 R/R AML

   - Subjects who have treatment failure to prior AML therapy (defined as failure to achieve at least CRi) or have relapsed after prior AML therapy, and
   - f πu–xvnβ(: D(xt Δβ(old

   Part 2

   - Cohort 1 R/R AML (same as Part 1)
   - Cohort 2 Subjects with newly diagnosed AML who are ineligible for intensive induction chemotherapy. Subjects must have had no prior AML treatment, with the exceptions of therapy for antecedent hematologic malignancies (eg, azacitidine for MDS) or hydroxyurea.
     a. Subjects 75 years old, OR
     b. Subjects between 18 and 74 years old (inclusive) with at least one of the following comorbidities:

        ECOG Performance Status of 3;

        Cardiac history of congestive heart failure (CHF) requiring treatment, left ventricular ejection fraction (LVEF) 50%, or chronic stable angina;

        Diffusing capacity of the lung for carbon monoxide (DLCO) 65% or forced expiratory volume in 1 second (FEV1) 65%;

        Any other comorbidity that the Investigator judges to be incompatible with intensive chemotherapy must be reviewed by the Sponsor Medical Monitor during screening and before study enrollment.

   Note: In both Part 1 and Part 2, subjects with a known record of FLT3-ITD mutant AML within the last 30 days from informed consent based on local testing can enroll in the study. FLT3-ITD status will be tested in a central laboratory for confirmation of eligibility, and any results indicating absence of FLT3-ITD will be communicated to the Investigator for possible discontinuation of the subject from study participation if ongoing clinical benefit is not observed. Subjects in Part 2 who do not show confirmation of FLT3-ITD mutation by central laboratory testing will be replaced. However, those who are deriving clinical benefit may be allowed to continue treatment.

2. Has an ECOG Performance Status (Section 17.9):

   In Part 1 and Part 2 Cohort 1 (subjects with R/R AML):

   - 0 to 2 for subjects 18 years old

   In Part 2 Cohort 2 (subjects with newly diagnosed AML):

   - 0 to 2 for subjects 75 years old
   - 0 to 3 for subjects between 18 and 74 years old (inclusive)

3. Has adequate renal function, defined as creatinine clearance 60 mL/min, as calculated using the modified Cockcroft-Gault equation ([{140 age in years} × {actual weight in kg}] divided by [{72 × serum creatinine in mg/dL}] multiply by 0.85 if female), OR if creatinine clearance 50-60 mL/min AND ≤t β(βxΔπ' (vΔxt ηx,,≥,,x(: 7A((upper limit of normal (ULN) (in obese subjects, the lean body weight can be used in the equation instead of actual body weight).
4. Has electrolyte levels (including those for potassium, calcium, and magnesium) within normal limits.
5. f xΔπ' (Mf g(t „w(M[g(; 7A× ULN (5 × ULN if deemed elevated due to leukemia).
6. Serum total bilirubin : 7A((h [a (1 =((h [a (≥y(wxx' xw(x'x t ηxw(wπx(η–('xπ"x' ≥t(–Δ≤,, βπu–xvηβ(≥η≤(w–vπ' x„,ηxw(S≥'uxΔηβ(f „wΔ–' x2.
7. Discontinuation of prior AML treatment before the start of study treatment (except hydroxyurea to control leukocytosis) for at least 2 weeks for cytotoxic agents, or for at least 5 half-lives for non-cytotoxic agents. Hydroxyurea is allowed until 48 hours prior to start of the study treatment.
8. Subject, if female of childbearing potential, must have a negative serum pregnancy test upon entry into this study and must be willing to use highly effective birth control (as defined in Section 17.7) during the period of therapy and for 6 months following the last investigational drug dose. A female is considered of childbearing potential following menarche and until becoming postmenopausal (no menstrual period for a minimum of 12 months), unless permanently sterile (undergone a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or confirmed by follicle stimulating hormone (FSH) test. If male, must be surgically sterile or be willing to use 1 form of highly effective contraception method upon enrollment, during the course of the study, and for 6 months following the last investigational drug dose.
9. Willingness to abstain from grapefruit/grapefruit juice and Seville oranges from 7 days before the first dose of study drug on Day 1 until the end of the study.
10. Able and willing to provide bone marrow biopsies/aspirates and buccal swab/saliva for PGx testing as requested by the protocol.

4.2. Exclusion Criteria

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

1. Presence of central nervous system (CNS) involvement of leukemia. Patients with a history of CNS leukemia may be eligible if the CNS leukemia is adequately controlled (defined as no active clinical symptoms of CNS disease and at least 2 consecutive lumbar punctures with no evidence of disease prior to study enrollment) after discussion with the Sponsor Medical Monitor.
2. Acute promyelocytic leukemia (AML subtype M3).
3. Has other concurrent malignancy that required systemic antineoplastic treatment within the previous 2 years, except for localized cancers that have apparently been cured (eg, non-melanoma skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast).
4. Uncontrolled or significant cardiovascular disease, including:
    a. QTcF interval >450 ms (average of triplicate determinations).
    b. Bradycardia of less than 50 bpm unless the subject has a pacemaker.
    c. Diagnosed or suspected long QT syndrome, or known family history of long QT syndrome.
    d. History of clinically relevant ventricular arrhythmias, such as ventricular tachycardia, ventricular fibrillation, or torsade de pointes.
    e. History of second or third degree heart block. Subjects 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.
    f. Myocardial infarction within 6 months prior to Screening.
    g. Uncontrolled angina pectoris within 6 months prior to Screening.
    h. New York Heart Association (NYHA) Class III or IV congestive heart failure (Section 17.10).
    i. Known [i QR(50% or institutional lower limit of normal.

        As an exception, subjects with newly diagnosed AML between 18 and 74 years old (inclusive) ≥,(c t Δ(; (O−≤−Δ(; (≥ɳ≤([i QR(A9. (−Δ(≥,βɳ≥ɳutional lower limit of normal will be eligible.

    j. Known DLCO 65% or FEV1 65%.

        As an exception, subjects with newly diagnosed AML between 18 and 74 years old (inclusive) in Part 2 Cohort 2 ≥ɳ≤(P [Ob (BA (−ΔRQi : (BA (will be eligible.

    k. Uncontrolled hypertension.
    l. Left bundle branch block.
5. Has an uncontrolled infection requiring intravenous antibiotics, antivirals, or antifungals.

6. Has known human immunodeficiency virus infection that is uncontrolled (increasing plasma HIV RNA viral load) with medication, or active hepatitis B or C infection based on positive tests during Screening.
7. Persistent, clinically significant >Grade 1 non-hematologic toxicity from prior AML therapies.
8. Pregnant or breast feeding.
9. Receiving drugs that are strong inducers of CYP3A or consπ’ ×ηΣ–„(–y(f η(V–≤„ β(j −Δη((hypericin) within 14 days prior to the first dose and during treatment.
10. Received anti-AML therapy (except for hydroxyurea) within the following washout periods before starting study medication:

    Seven days OR 5 half-lives, whichever is longer, for small molecule drugs.

    Twenty-one days OR 5 half-lives, whichever is shorter, for antibody-based, immune-based, biologic, or cellular therapies.
11. Has received allogeneic hematopoietic cell transplantation (HCT) within 60 days of the first dose of study drugs.
12. Clinically significant graft versus host disease (GVHD) or GVHD requiring initiation of systemic treatment or systemic treatment escalation within 21 days prior to Screening and/or >Grade 1 persistent or clinically significant non-hematologic toxicity related to HCT.
13. Medical condition, serious intercurrent illness, or other circumstance that, in the Investigator β(–πwz’ x„,ηƒ(v–π’w(–x–×t Δw≥ x(ηΣx(vt „,w≥wt ηx β(βt yxη (t β(t (βηπw (βπu–xvnƒ(–Δ(ηΣt η(could interfere with study objectives.
14. Prior treatment with MDM2 inhibitors.

Additional exclusion criterion for the Part 2 Cohort 1 subgroup of 12 subjects for the DDI substudy

15. Receiving drugs that are strong CYP3A inhibitors within 7 days OR 5 terminal half-lives, whichever is longer, prior to the first dose and until completion of 2 cycles of treatment.

5. STUDY TREATMENT(S)

5.1. Assigning Subjects to Treatments and Blinding

Both parts of the study are open-label and no blinding will be performed.

5.2. Study Drug(s)

5.2.1. Description

Quizartinib is a small molecule inhibitor of FLT3. The drug is supplied as tablets in strengths of 20 mg quizartinib hydrochloride (17.7 mg free base) and 30 mg quizartinib hydrochloride (26.5 mg free base) for oral administration.

Milademetan is a small molecule inhibitor of MDM2-p53 interaction that activates p53 pathway. The drug is supplied as capsules in strengths of 5 mg, 20 mg, 30 mg, 45 mg, 80 mg, 100 mg, and 200 mg for oral administration. The indicated capsule strengths are equivalent to the amount of free base (DS-3032a).

Milademetan (DS-3032a) is the free base and the active moiety of the salt form (DS-3032b). The salt form (DS-3032b) is the active pharmaceutical ingredient of the oral capsule formulation. Throughout the remainder of this document, DS-3032a and DS-3032b will be referred to as ’ ≥t wx’ xηt „ (π„’xββ(≥„w≥vt ηxw(−η≤x∆ ≥βx7

The 2 investigational drugs will be administered in combination as indicated in the dose escalation and dose expansion parts of the study. Quizartinib and milademetan may be administered without regard to the timing of food, except as noted for the DDI substudy.

5.2.2. Labeling and Packaging

Milademetan 5 mg, 20 mg, 80 mg, and 200 mg capsules will be supplied in labeled blister cards (wallets), each containing 7 capsules; milademetan 30 mg and 100 mg capsules will be supplied in labeled high-density polyethylene (HDPE) bottles with a child-resistant cap, and each bottle will contain 35 capsules. Quizartinib will be supplied in labeled HDPE bottles with a child-resistant cap and each bottle will contain 30 tablets. The blister label and the bottle label will include all information required by national and local regulations.

5.2.3. Preparation

Study drug will be provided to sites as fully prepared blister cards (wallets) and bottles. Blister cards (wallets) and bottles will be individually numbered. Assignment of blister cards (wallets) and bottles to subjects will be done via the Interactive Web/Voice Response System (IXRS).

5.2.4. Administration

Quizartinib will be administered orally qd.

Milademetan will be administered on Days 1 to 14 of every 28 day cycle. Alternative dosing schedules in 28 day cycles may be used for milademetan (eg, qd 7/28 and qd 3/14 × 2) based on emerging safety and efficacy data.

Quizartinib and milademetan may be administered without regard to the timing of food, except in the DDI substudy, where quizartinib and milademetan will be dosed on an empty stomach (no food for at least 2 hours pre-dose and 1 hour post-dose) on Cycle 1/Day 1, Cycle 1/Day 28,

Cycle 2/Day 1, and Cycle 2/Day 14. In the DDI substudy, subjects will also be required to fast for 2 additional hours post-dose.

Milademetan and quizartinib administration that occurs at clinic visits will be supervised by a member of the site staff.

5.2.5. Storage

Drug supplies must be stored in a secure, limited access storage area under the recommended storage conditions. The required storage conditions are clearly depicted on the drug label.

If storage conditions are not maintained per specified requirements, Covance or Daiichi Sankyo, Inc. (hereinafter referred to as Daiichi Sankyo) should be contacted.

5.2.6. Drug Accountability

When a drug shipment is received, the Investigator or designee will check the amount and condition of the drug, check for appropriate local language in the label, and drug expiration date.

In addition, the Investigator or designee shall contact the Sponsor as soon as possible if there is a problem with the shipment.

A Drug Accountability Record will be provided for the study drugs milademetan and quizartinib. The record must be kept current and should contain the dates and quantities of study drug Δxvx≥ xw5(βπu-xvη β(≥wx„ηy≥vt η≥„(„π' uxΔ(and/or initials or supply number (as applicable) for whom the study drug was dispensed, the date and quantity of study drug dispensed and remaining, as well as the initials of the dispenser.

Study drugs will be returned or destroyed locally only after the study monitor has completed a final inventory to verify the quantity to be returned. The return of study drug must be documented and the documentation included in the shipment. At the end of the study, a final study drug reconciliation statement for milademetan and quizartinib must be completed by the Investigator or designee and provided to the Sponsor. Unused drug supplies may be destroyed by the Investigator when approved in writing by the Sponsor and Sponsor has received copies of the study site β(wΔπz(≤t „w'≥„z(t „w(w≥β×-β≥η≥„(standard operating procedures (SOPs) and it is assured that the Sponsor will receive copies of the certificate of destruction which is traceable to the study drugs. Destruction of the study drugs at the site is preferred.

5.3. Control Treatment

This is a single arm study and there is no control treatment.

5.4. Dose Interruptions and Reductions

Dose interruptions and/or dose reductions are allowed based on safety and clinical benefit. QTcF prolongation and non-hematologic toxicities may result in the dose reduction or dose interruption of quizartinib and/or milademetan.

5.4.1. Dose Interruptions and Reductions For QTcF Prolongation

The following dose interruptions and/or reductions will be made for QTcF prolongation:

QTcF average of triplicate readings >480 ms η┤(500 ms

- Quizartinib dose will be reduced by 1 level without interruption, eg, from 60 mg to 40 mg, from 40 mg to 30 mg, and from 30 mg to 20 mg, depending on the dose at which the QT prolongation occurred. If the QTcF prolongation occurs at 20 mg, then quizartinib will be discontinued.

QTcF average of triplicate readings >500 ms

- Quizartinib dosing will be interrupted for up to 14 days. If QTcF returns to within 30 ms −y(ut βx'≥,x(−Δ(>A9(ms within 14 days, treatment may be resumed at a reduced dose (eg, from 60 mg to 40 mg, from 40 mg to 30 mg, and from 30 mg to 20 mg), depending on the dose at which the QT prolongation occurred.
- If QTcF prolongation is >500 ms and recurs despite appropriate dose reductions and correction/elimination of other risk factors (eg, serum electrolyte abnormalities, concomitant QT prolonging medication), the subject will be permanently discontinued from quizartinib.

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

- Quizartinib will be discontinued.

5.4.1.1. Managing QTc Prolongation

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.

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

5.4.1.2. Managing Electrolyte Abnormalities

Electrolytes, including potassium, calcium and magnesium, must be within normal limits prior to the commencement of each cycle.

Hypokalemia should be managed with oral or IV potassium supplementation, as clinically indicated, and serial potassium level monitoring should be performed until potassium levels normalize. Serum potassium should be maintained between 3.5 mEq/L to 5.0 mEq/L (3.5 mmol/L to 5.0 mmol/L).

Appropriate management should include reduction of serum electrolyte losses, replacement of electrolyte stores, and evaluation and treatment of associated toxicities. If possible, the underlying cause of hypokalemia should be investigated to prevent further episodes. Electrocardiograms should be monitored and magnesium should be replaced if there is concomitant hypomagnesemia. Serum magnesium should be maintained between 1.5 mEq/L to 2.5 mEq/L (0.75 mmol/L to 1.25 mmol/L) and total serum calcium should be maintained between 8.5 mg/dL to 10.2 mg/dL (2.18 mmol/L to 2.58 mmol/L).

If Grade 3 hypokalemia occurs (potassium <3.0 mmol/L to 2.5 mmol/L), IV potassium replacement, close subject follow-up, continuous ECG monitoring, and serial potassium levels every 2 to 4 hours until recovery to Grade 1 (<lower limit of normal to 3.0 mmol/L) should be considered.

5.4.1.3. Managing Nausea and Vomiting

Established nausea and vomiting should be managed to the fullest extent possible. Acceptable non-QT-prolonging agents such as aprepitant, metoclopramide, fosaprepitant, and droperidol can be administered.[18]

5.4.2. Dose Interruptions and Reductions For Non-hematologic Toxicities

The following guidelines should be followed for subjects who develop a Grade 3 or 4 non-hematologic toxicity that is at least possibly related to study drug(s) and persisting >48 hours ≥ηΕ¬πη(≥’ ×Δ¬ x’ x,,η(η¬(Grade 2 or without waiting 48 hours if in the Investigators judgment the AE poses a serious risk to the subject:

Dosing will be interrupted for up to 28 days.

- Uψ(η¬ ≥ν≥η (≥’ ×Δ¬ xβ(η¬(Grade 1 within 28 days, treatment may be resumed at the previous dose.
- If toxicity improves to Grade 2 within 28 days, treatment may be resumed at a reduced dose (1 level below) for milademetan and/or quizartinib only after the toxicity has resolved to <Grade 2 (Grade 1 or less). Optionally for milademetan, the Investigator after consultation with the Sponsor Medical Monitor may reduce the dose frequency (eg, 10/28 days, or 7/28 days, or 3/14 days × 2) in Cycle 2 or subsequent cycles while maintaining the same daily dose of milademetan.
- If toxicity does not improve/resolve within 28 days, then treatment may be discontinued after discussion between the Investigator and Sponsor Medical Monitor.

5.4.3. Dose Interruptions and Reductions for Hematologic Toxicities

Active monitoring and appropriate treatment should be employed for neutropenia and thrombocytopenia. For myelosuppression not related to underlying AML (ANC <0.5 × 10^9/L and/or platelet count <50 × 10^9/L):

If toxicities persist, the Investigator should discuss with the Sponsor prior to any additional dose reductions of either quizartinib or milademetan.

Reduce the dose of milademetan by 1 level.

For milademetan, the Investigator should consult with the Sponsor Medical Monitor:

Reduce the dose frequency (eg, 10/28 days, or 7/28 days, or 3/14 days × 2) while keeping the same dose level, OR

Reduce the dose of milademetan by 1 dose level while keeping the same dosing schedule

When the subject is no longer myelosuppressed, both study drugs may be resumed at the previous dose and/or dosing schedule.

5.4.4. Dose Reductions With Concomitant Administration of a Strong CYP3A Inhibitor

The following dose reductions will be performed with the concomitant administration of a strong CYP3A inhibitor:

Quizartinib:

- 60 mg dose will be reduced to 30 mg
- 30 mg and 40 mg doses will be reduced to 20 mg
    - Consequently, quizartinib 30 mg lead-in to 60 mg will be reduced to a 20 mg lead-in to 30 mg

Milademetan:

- Dose will be reduced to half of the prescribed dose (ie, 90-mg, 120-mg, and 160-mg doses of milademetan will be reduced to 45 mg, 60 mg, and 80 mg, respectively)

Resumption of regularly scheduled doses of quizartinib and milademetan after discontinuation of strong CYP3A inhibitor should be as follows:

Quizartinib: Resume regularly scheduled dose the day following discontinuation

Milademetan: Resume regularly scheduled dose after a 3-day washout period following discontinuation

5.5. Method of Assessing Treatment Compliance

The following measures will be employed to ensure treatment compliance during dosing at the clinical site:

Milademetan and quizartinib dispensed only to subjects participating in the study and complying with the instructions from the clinical study personnel.

In regions where at-home dosing of study drugs is required, milademetan and quizartinib may be dispensed in amounts exceeding the minimum amount required for the period of time until the next visit. Subjects will be instructed to bring back to the site all unused milademetan and quizartinib at the next visit. Alternatively, to ensure compliance, the site personnel may choose to dispense only the adequate amount of study drug required until the next scheduled visit. Compliance with the study drug regimen will be determined by counting unused capsules returned and reviewing the pill diary provided to the subjects to fill in.

Milademetan and quizartinib administration that occurs at clinic visits will be supervised by a member of the site staff.

5.6. Prior and Concomitant Medications

5.6.1. Prior Medication

All non-cancer medications received by subjects within 30 days prior to Screening will be recorded as prior medications.

All anti-cancer medications that the subject received at any point, irrespective of the time relative to screening, will be recorded from the medical history.

5.6.2. Concomitant Medication (Drugs and Therapies)

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

Information on concomitant medications will be collected from the time of informed consent through 30 days after the last dose of study treatment (does not apply to the allogeneic HCT period until the subject is able to return to the site). Data collected will include medication name, indication, dose, start date, and stop date.

Concomitant use of non-anticancer medications that are not inducers of CYP3A are allowed (refer to Section 17.6).

Concomitant use of anticancer medications, and drugs, herbs or fruits that are strong inducers of CYP3A are prohibited. Grapefruit/grapefruit juice and Seville oranges are prohibited 7 days before the first dose of study drug and during treatment. St V–≤,, β(Wort (hypericin) will not be permitted for 14 days prior to the first dose and during treatment.

Concomitant medications that prolong the QT/QTc interval are prohibited (refer to Section 17.6). Exceptions are made for antibiotics and antifungals that are used as standard of care for the prevention or treatment of infections or if the Investigator believes that beginning therapy with a potentially QTc-prolonging medication is vital to an individual βπu–xvη β care while on study.

Proton pump inhibitors and other gastric pH modifiers should be avoided, except locally acting antacids that can be administered in the window of 2 hours before or after quizartinib and milademetan administration.

Hydroxyurea is permitted for control of leukocytosis during Screening, but should be discontinued 48 hours prior to start of study treatment. However, hydroxyurea can be re-started in Cycle 1 as clinically necessary up to a maximum of 8 days and up to a maximum dose of 5 g/day. If there is a clinical need to administer hydroxyurea for longer than 8 days or beyond Cycle 1 that should be discussed between the Investigator and Sponsor Medical Monitor.

5.7. Discontinuation

A subject may discontinue from study drug treatment, but may agree to receive long-term follow-up phone calls.

5.7.1. Study Drug Discontinuation

The following reasons are considered sufficient to discontinue a subject from study drug treatment:

AE

Death

PD or relapse which meets protocol-defined response criteria (Section 17.4)

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Allogeneic HCT

Pregnancy

Protocol deviation

Lost to follow-up

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Other (the reason should be discussed between the Investigator and Sponsor Medical Monitor, and should be recorded on the case report form [CRF])

All subjects discontinued from study treatment due to any reason other than withdrawal of consent for follow-up will undergo assessment at follow-up visits.

If the subject discontinues study treatment due to an AE, the Investigator will follow the subject until the AE has resolved or stabilized, or until the subject is available for follow-up.

Response criteria-met or clinical PD/relapse is considered a sufficient reason to discontinue study drug treatment; however, the Investigator may continue the subject on study drug treatment until the Investigator has determined alternative AML therapies and considers the study drug treatment to be no longer beneficial to the subject. The decision to discontinue a subject from study drug treatment remains the responsibility of the Investigator and should not be delayed or refused by the Sponsor.

When one of the study drugs is discontinued due to toxicities, Investigators may continue the other study drug if this is considered to be safe and in the best interest of the subject after consultation with the Sponsor Medical Monitor.

5.7.2. Study Discontinuation

If a subject is withdrawn from the study (eg, has completed the 30-day safety window and withdrawn consent for receiving long-term follow-up, or has proceeded to next treatment regimen), the Investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal, including the date of last treatment and the reason for withdrawal.

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

Subjects may be withdrawn from the study at any time after signing the Informed Consent Form (ICF) for the following reasons:

Withdrawal by subject β(wxv≥β≥−„

Death

PD or relapse

Lost to follow-up

Other (the reason should be specified on the CRF)

5.7.3. Subject Replacement

For a subject to be considered evaluable for DLT, the subject must have received at least 75% of the prescribed Cycle 1 doses and completed safety assessments of the DLT evaluation period or experienced a DLT in this period. Subjects who are unable to complete at least 75% of prescribed Cycle 1 doses of milademetan and quizartinib or unable to be evaluated for safety during the DLT evaluation period as a result of unequivocal progression of disease or non-compliance may be replaced.

In both Part 1 and Part 2, subjects with a known record of FLT3-ITD mutant AML within the last 30 days from informed consent based on local testing can enroll in the study. However, FLT3-ITD status will be tested in a central laboratory for confirmation of eligibility and any results indicating absence of FLT3-ITD will be communicated to the Investigator for possible discontinuation of the subject from study participation if ongoing clinical benefit is not observed. Subjects in Part 2 who do not show confirmation of FLT3-ITD mutation by central laboratory testing will be replaced. However, those who are deriving clinical benefit may be allowed to continue treatment.

5.7.4. Subject Re-screening Procedures

Re-screening is permitted for any subject who failed to meet eligibility criteria upon initial screening. The subject identification number must remain the same at the time of re-screening. The initial screening information and the reason why the subject is ineligible for the initial evaluation will be recorded on the Screening Log. If the subject successfully repeats the failed initial screening assessment(s) within the 14-day Screening period, the subject may be enrolled. No other data from the initial screening will be entered into the clinical database for a subject who is re-screened. If performing an echocardiogram (ECHO) or multigated acquisition (MUGA) scan is not possible during screening, an LVEF value from an ECHO/MUGA performed within 60 days before the first dose of study drugs can be used for eligibility determination if no changes in cardiac conditions were observed based on the I,, xβηzt η−Δβ(clinical assessment.

6. STUDY PROCEDURES

A study visit schedule in tabular format is provided in the Schedule of Events tables (Section 17.3). Throughout the treatment period, serum pregnancy tests are to be done as indicated for women of childbearing potential. P x×x„w≥„z(−„(η≤x(βηw (β≥ηx β(Δxz≥−„(lxz5h f 25(βηw (wΔtzs and a pill diary may be dispensed for at-home study drug dosing, as noted in the study procedures and in the Schedule of Events tables.

6.1. Screening

6.1.1. Part 1 (Dose Escalation) and Part 2 (Dose Expansion), Screening (Pre-cycle)

The screening (Pre-cycle) period occurs within 14 days prior to starting study therapy for Part 1 and Part 2 (except subjects in the DDI substudy) and within 15 days prior to starting study therapy for Part 2 (DDI substudy). The following procedures will be performed during the Part 1 and Part 2 screening periods:

Obtain written (ie, signed and dated) informed consent.

Assign a subject identifier number.

Record demographic, medical history information including AML and antecedent hematologic disorder, and prior AML therapy history (ie, best response, relapse date).

Perform a complete physical examination and record weight and height.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Assess functional status using the ECOG Performance Status Scale.

Obtain blood samples for safety laboratories (hematology and serum chemistry).

Obtain blood sample for testing active hepatitis B or C infection.

Obtain blood sample for testing FLT3 mutation.

Obtain a serum sample for pregnancy testing in women of childbearing potential.

Obtain an FSH test in women of childbearing potential to confirm menarche.

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Measure LVEF by either ECHO or MUGA.

Record prior (within 30 days of consent) and current medications.

Transfusion history (type, date of transfusion, number of units) for the 56 days prior to first dose date of study drugs (first day exclusive).

Assess subjects for AEs.

Obtain bone marrow biopsies/aspirates for disease assessment and biomarker tests.

Note: Submission of bone marrow specimens is required for biomarker tests (see details in Section 7.1.1.1 and instructions in the Laboratory Manual).

Complete the Inclusion/Exclusion Criteria Form for subject registration.

- The Sponsor (and/or Contract Research Organization [CRO]) will perform registration after verifying that the subject meets the inclusion/exclusion criteria (Sections 4.1 and 4.2) provided by the Investigator. If the Sponsor has any questions regarding the information sent by the Investigator, he or she will immediately contact the Investigator to check the details. Directly after registration, the Sponsor will forward the results of registration to the Investigator.
- The Investigator must not prescribe or administer the study drug until the subject has completed registration. If the Sponsor disqualifies a subject from participation in the clinical study, the Investigator will be notified. The Investigator will then explain this outcome to the relevant subject.

6.2. Randomization

Not applicable.

6.3. Treatment Period

6.3.1. Part 1 (Dose Escalation)

Unless otherwise stated, an activity occurs before study drug administration.

6.3.1.1. Part 1 (Dose Escalation), Cycle 1/Day 1

The following procedures will be completed pre-dose during the Part 1, Cycle 1/Day 1 visit. If the Screening visit for Part 1 is completed within 24 hours of Cycle 1/Day 1, the assessments need not be repeated, with the exception of ECOG Performance Status Scale, vital signs, and 12-lead ECG. Blood samples for safety laboratory tests need not be collected if previously collected within 72 hours of Cycle 1/Day 1.

Perform a complete physical examination and record weight.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Assess functional status using the ECOG Performance Status Scale.

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Obtain a blood sample for PK measurements.

Obtain blood samples for exploratory biomarkers.

Obtain a blood sample for banking plasma.

Obtain a blood sample for serum MIC-1 analysis.

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Obtain a buccal swab or saliva for pharmacogenomics (PGx).

Informed consent specifically allowing PGx testing sample storage must be obtained before collecting sample.

Administer milademetan per protocol.

Administer quizartinib per protocol.

The following procedures will be completed post-dose during the Part 1, Cycle 1/Day 1 visit:

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) at 3 hours (± 10 minutes) post-dose.

Perform a 12-lead ECG in triplicate at 1, 2, 4, and 6 hours post-dose as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain a blood sample for PK measurements at the following timepoints: 0.5, 1, 2, 3, 4, and 6-8 hours post-dose as indicated in Section 8.

6.3.1.2. Part 1 (Dose Escalation), Cycle 1/Day 2

The following procedures will be performed pre-dose during the Part 1, Cycle 1/Day 2 visit:

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Obtain blood samples for exploratory biomarkers.

Obtain a blood sample for serum MIC-1 analysis.

Obtain a blood sample for PK measurements.

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer milademetan per protocol.

Administer quizartinib per protocol.

Dispense milademetan per protocol (to take home, if regionally required).

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense a pill diary with dose administration instructions (for at-home dosing, if regionally required).

6.3.1.3. Part 1 (Dose Escalation), Cycle 1/Day 8

The following procedures will be performed pre-dose during the Part 1, Cycle 1/Day 8 visit (± 2 days):

Perform a complete physical examination and record weight.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Assess functional status using the ECOG Performance Status Scale.

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Obtain blood samples for exploratory biomarkers.

Obtain a blood sample for serum MIC-1 analysis.

Obtain a blood sample for PK measurements.

Obtain a blood sample for banking plasma.

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer milademetan per protocol. (Not administered if subject is in the qd 7/28 or qd 3/14 × 2 schedule).

Administer quizartinib per protocol.

Dispense milademetan per protocol (to take home, if regionally required). (Not dispensed if subject is in the qd 7/28 or qd 3/14 × 2 schedule).

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense and review pill diary (for at-home dosing, if regionally required) and assess treatment compliance.

6.3.1.4. Part 1 (Dose Escalation), Cycle 1/Day 14

The following procedures will be completed pre-dose during the Part 1, Cycle 1/Day 14 visit:

Perform a complete physical examination and record weight.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Assess functional status using the ECOG Performance Status Scale.

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Obtain a blood sample for serum MIC-1 analysis.

Obtain a blood sample for PK measurements.

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer milademetan per protocol. (Not administered if subject is in the qd 7/28 or qd 3/14 × 2 schedule).

Administer quizartinib per protocol.

Dispense and review pill diary (for at-home dosing, if regionally required) and assess treatment compliance.

The following procedures will be completed post-dose during the Part 1, Cycle 1/Day 14 visit:

Perform a 12-lead ECG in triplicate at 1, 2, 4, and 6 hours post-dose as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain a blood sample for PK measurements at the following timepoints: 0.5, 1, 2, 3, 4, and 6-8 hours post-dose as indicated in Section 8.

For 60 mg quizartinib cohorts, determine whether the QTcF allows for escalating the quizartinib dose to 60 mg for Day 15 onwards.

6.3.1.5. Part 1 (Dose Escalation), Cycle 1/Day 15

The following procedures will be completed pre-dose during the Part 1, Cycle 1/Day 15 visit:

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain a blood sample for PK measurements.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer quizartinib per protocol.

Administer milademetan per protocol if subject is in the qd 3/14 × 2 dosing schedule.

The following procedures will be completed post-dose during the Part 1, Cycle 1/Day 15 visit:

Perform a 12-lead ECG in triplicate at 3 hours post-dose as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain a blood sample for PK measurements at 3 hours post-dose as indicated in Section 8.

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense milademetan per protocol if subject is in the qd 3/14 × 2 dosing schedule.

6.3.1.6. Part 1 (Dose Escalation), Cycle 1/Day 22

The following procedures will be completed pre-dose during the Part 1, Cycle 1/Day 22 visit (± 2 days):

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Obtain a blood sample for serum MIC-1 analysis.

Obtain a blood sample for PK measurements.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer quizartinib per protocol.

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense and review pill diary (for at-home dosing, if regionally required) and assess treatment compliance.

The following procedures will be completed post-dose during the Part 1, Cycle 1/Day 22 visit:

Perform a 12-lead ECG in triplicate at 3 hours post-dose as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain a blood sample for PK measurements at 3 hours post-dose as indicated in Section 8.

6.3.1.7. Part 1 (Dose Escalation), Cycle 2/Day 1

The following procedures will be completed pre-dose during the Part 1, Cycle 2/Day 1 visit (± 2 days):

Perform a complete physical examination and record weight.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Assess functional status using the ECOG Performance Status Scale.

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain a blood sample for PK measurements.

Obtain bone marrow biopsies/aspirates for disease assessment and biomarker tests.

Note: Submission of bone marrow specimens is required for biomarker tests (see details in Section 7.1.1.1 and instructions in the Laboratory Manual). Additionally, submission of bone marrow samples for MRD analysis is required if <5% blasts in bone marrow is observed.

Obtain blood samples for exploratory biomarkers.

Obtain a blood sample for banking plasma.

Obtain a blood sample for serum MIC-1 analysis.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer milademetan per protocol.

Administer quizartinib per protocol.

Dispense milademetan per protocol (to take home, if regionally required).

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense and review pill diary (for at-home dosing, if regionally required) and assess treatment compliance.

The following procedures will be completed post-dose during the Part 1, Cycle 2/Day 1 visit:

Perform a 12-lead ECG in triplicate at 3 hours post-dose as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain a blood sample for PK measurements at 3 hours post-dose as indicated in Section 8.

6.3.1.8. Part 1 (Dose Escalation), Cycle 2/Day 8

The following procedures will be completed pre-dose during the Part 1, Cycle 2/Day 8 visit (± 2 days):

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain a blood sample for PK measurements.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer milademetan per protocol if subject is in the qd 14/28 dosing schedule.

Administer quizartinib per protocol.

Dispense milademetan per protocol (to take home, if regionally required) if subject is in the qd 14/28 dosing schedule.

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense and review pill diary (for at-home dosing, if regionally required) and assess treatment compliance.

6.3.1.9. Part 1 (Dose Escalation), Cycle 2/Day 15

The following procedures will be completed pre-dose during the Part 1, Cycle 2/Day 15 visit (± 2 days):

Perform a complete physical examination and record weight.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Assess functional status using the ECOG Performance Status Scale.

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain a blood sample for PK measurements.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer quizartinib per protocol.

Administer milademetan per protocol if subject is in the qd 3/14 × 2 dosing schedule.

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense milademetan per protocol if subject is in the qd 3/14 × 2 dosing schedule.

Dispense and review pill diary (for at-home dosing, if regionally required) and assess treatment compliance.

6.3.1.10. Part 1 (Dose Escalation), Cycle 2/Day 22

The following procedures will be completed pre-dose during the Part 1, Cycle 2/Day 22 visit (± 2 days):

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain a blood sample for PK measurements.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer quizartinib per protocol.

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense and review pill diary (for at-home dosing, if regionally required) and assess treatment compliance.

6.3.1.11. Part 1 (Dose Escalation), Cycle 3/Day 1

The following procedures will be completed pre-dose during the Part 1, Cycle 3/Day 1 visit (± 4 days):

Perform a complete physical examination and record weight.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Assess functional status using the ECOG Performance Status Scale.

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Obtain a serum sample for pregnancy testing in women of childbearing potential.

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain a blood sample for PK measurements.

Obtain bone marrow biopsies/aspirates for disease assessment and biomarker tests.

> **Note:** Submission of bone marrow specimens is required for biomarker tests (see details in Section 7.1.1.1 and instructions in the Laboratory Manual). Additionally, submission of bone marrow samples for MRD analysis is required if <5% blasts in bone marrow is observed.

Obtain blood samples for exploratory biomarkers.

Obtain a blood sample for banking plasma.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer milademetan per protocol.

Administer quizartinib per protocol.

Dispense mlademetan per protocol (to take home, if regionally required).

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense and review pill diary (for at-home dosing, if regionally required) and assess treatment compliance.

The following procedures will be completed post-dose during the Part 1, Cycle 3/Day 1 visit:

Perform a 12-lead ECG in triplicate at 3 hours post-dose as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain a blood sample for PK measurements at 3 hours post-dose as indicated in Section 8.

6.3.1.12. Part 1 (Dose Escalation), Cycle 3/Days 8, 15, and 22

The following procedures will be completed pre-dose during the Part 1, Cycle 3/Days 8, 15, and 22 visits (± 4 days):

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain a blood sample for PK measurements.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer mlademetan per protocol only on Part 1, Cycle 3/Day 8 visit if subject is in the qd 14/28 dosing schedule and only on Part 1, Cycle 3/Day 15 visit if subject is in qd 3/14 × 2 dosing schedule (no administration of mlademetan for subjects in the qd 7/28 dosing schedule).

Administer quizartinib per protocol.

Dispense mlademetan per protocol (to take home, if regionally required) only on Part 1, Cycle 3/Day 8 visit if subject is in the qd 14/28 dosing schedule and only on Part 1, Cycle 3/Day 15 visit if subject is in the qd 3/14 × 2 dosing schedule (no dispensing of mlademetan for subjects in the qd 7/28 dosing schedule).

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense and review pill diary (for at-home dosing, if regionally required) and assess treatment compliance.

6.3.1.13. Part 1 (Dose Escalation), Day 1 of Cycle 4 and All Subsequent Cycles

The following procedures will be performed pre-dose during the Part 1, Cycle 4/Day 1 (± 4 days), and all subsequent cycles on Day 1 (± 4 days):

Perform a complete physical examination and record weight.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Assess functional status using the ECOG Performance Status Scale.

Obtain blood samples for safety laboratory tests (hematology and serum chemistry). In subjects who develop gastrointestinal (GI) AEs, such as vomiting and diarrhea of S Δt wx(2, blood chemistry and 12-lead ECGs will be assessed weekly or more frequently as clinically needed until the GI AEs and electrolyte abnormalities are Δxβ–" xw(η–(S Δt wx(1. In subjects with potassium, calcium, and magnesium Grade 1, blood chemistry and 12-lead ECGs will be assessed twice a week.

Obtain a serum sample for pregnancy testing in women of childbearing potential on Day 1 of every 3 cycles from Cycle 3 (ie, Cycles 6, 9, 12, etc).

Perform a 12-lead ECG in triplicate up to Part 1, Cycle 6/Day 1 after subject has been in supine position for 5 minutes prior.

Obtain blood samples for PK measurements up to Part 1, Cycle 6/Day 1.

Obtain bone marrow biopsies/aspirates for disease assessment and biomarker tests (see details in Section 7.1.1 and instructions in the Laboratory Manual):

If subject achieves CR, CRi, or MLFS before Cycle 4/Day 1 (eg, CR on Cycle 3/Day 1), then bone marrow biopsies/aspirates will be not required on Cycle 4/Day 1.

- Perform bone marrow biopsies/aspirates on Day 1 of Cycles 6, 9, and 12 if subject remains in CR, CRi, or MLFS.
- If subject remains in CR, CRi, or MLFS on Cycle 12/Day 1, bone marrow biopsies/aspirates will be required at Day 1 of Cycles 18, 24, and every 6 cycles thereafter.

If subject does not achieve CR, CRi, or MLFS before Cycle 4/Day 1(eg, PR on Cycle 3/Day 1), then bone marrow biopsies/aspirates will be required on Cycle 4/Day 1 and on Day 1 of every cycle thereafter until subject achieves CR, CRi, or MLFS.

Unscheduled bone marrow biopsies/aspirates can be performed whenever clinically indicated.

Note: Submission of bone marrow specimens beyond Cycle 3/Day 1 is required at the following visits (see details in Section 7.1.1.1 and instructions in the Laboratory Manual):

Bone marrow samples on Day 1 of Cycles 6, 9, 12, 18, 24, and every 6 cycles thereafter.

Bone marrow sample from unscheduled bone marrow biopsies/aspirates when disease progression (relapse or progressive disease) is suspected.

Additionally, submission of bone marrow samples for MRD analysis (eg, flow cytometry and/or next generation sequencing) is required on the day when <5% blasts in bone marrow is observed and/or at the subsequent timepoints for bone marrow sample collection.

Bone marrow samples from other timepoints are not required to be submitted (eg, Cycle 4/Day1).

Obtain blood samples for plasma and exploratory biomarkers analyses (every 3 cycles after Cycle 3).

Obtain a blood sample for banking plasma (every 3 cycles after Cycle 2).

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer milademetan per protocol.

Administer quizartinib per protocol.

Dispense milademetan per protocol (to take home, if regionally required).

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense and review pill diary (for at-home dosing, if regionally required) and assess treatment compliance.

The following procedures will be completed post-dose during the Part 1, Cycles 4 to 6 on Day 1:

Perform a 12-lead ECG in triplicate at 3 hours post-dose up to Part 1, Cycle 6/Day 1 as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain blood samples for PK measurements at 3 hours post-dose up to Part 1, Cycle 6/Day 1 as indicated in Section 8.

6.3.2. Treatment Period, Part 2 (Dose Expansion), Except Subjects in the DDI Substudy

Unless otherwise stated, an activity occurs before study drug administration.

Note: Electrolytes, including potassium, calcium, and magnesium, must be within normal limits prior to the commencement of each cycle.

6.3.2.1. Part 2 (Dose Expansion), Cycle 1/Day 1

The following procedures will be completed pre-dose during the Part 2, Cycle 1/Day 1 visit. If the Screening visit for Part 2 is completed within 24 hours of Cycle 1/Day 1, the assessments need not be repeated, with the exception of ECOG Performance Status Scale, vital signs, and 12-lead ECG. Blood samples for safety laboratory tests need not be collected if previously collected within 72 hours of Cycle 1/Day 1.

Perform a complete physical examination and record weight.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Assess functional status using the ECOG Performance Status Scale.

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain a blood sample for PK.

Obtain blood samples for exploratory biomarkers.

Obtain a blood sample for banking plasma.

Obtain a blood sample for serum MIC-1 analysis.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Obtain a buccal swab or saliva for PGx.

Informed consent specifically allowing PGx testing sample storage must be obtained before collecting sample.

Administer milademetan per protocol.

Administer quizartinib per protocol.

The following procedures will be completed post-dose during the Part 2, Cycle 1/Day 1 visit:

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) at 3 hours (± 10 minutes) post-dose.

Perform a 12-lead ECG in triplicate at 3 hours post-dose as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain blood samples for PK measurements at 3 hours post-dose as indicated in Section 8.

6.3.2.2. Part 2 (Dose Expansion), Cycle 1/Day 2

The following procedures will be performed pre-dose during the Part 2, Cycle 1/Day 2 visits.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain a blood sample for PK measurements.

Obtain blood samples for exploratory biomarkers.

Obtain a blood sample for serum MIC-1 analysis.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer milademetan per protocol.

Administer quizartinib per protocol.

Dispense milademetan per protocol (to take home, if regionally required).

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense a pill diary with dose administration instructions (for at-home dosing, if regionally required).

6.3.2.3. Part 2 (Dose Expansion), Cycle 1/Day 8

The following procedures will be performed pre-dose during the Part 2, Cycle 1/Day 8 visits (± 2 days):

Perform a complete physical examination and record weight.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Assess functional status using the ECOG Performance Status Scale.

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain a blood sample for PK measurements.

Obtain blood samples for exploratory biomarkers.

Obtain a blood sample for banking plasma.

Obtain a blood sample for serum MIC-1 analysis.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer milademetan per protocol.

Administer quizartinib per protocol.

Dispense milademetan per protocol (to take home, if regionally required).

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense and review pill diary (for at-home dosing, if regionally required) and assess treatment compliance.

The following procedures will be completed post-dose during the Part 2, Cycle 1/Day 8 visits:

Perform a 12-lead ECG in triplicate at 3 hours post-dose as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain a blood sample for PK measurements at 3 hours post-dose as indicated in Section 8.

6.3.2.4. Part 2 (Dose Expansion), Cycle 1/Day 14

The following procedures will be completed pre-dose during the Part 2, Cycle 1/Day 14 visit:

Perform a complete physical examination and record weight.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Assess functional status using the ECOG Performance Status Scale.

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain a blood sample for PK measurements.

Obtain a blood sample for serum MIC-1 analysis.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer milademetan per protocol.

Administer quizartinib per protocol.

Dispense and review pill diary (for at-home dosing, if regionally required) and assess treatment compliance.

The following procedures will be completed post-dose during the Part 2, Cycle 1/Day 14 visit:

Perform a 12-lead ECG in triplicate at 3 hours post-dose as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain a blood sample for PK measurements at 3 hours post-dose as indicated in Section 8.

6.3.2.5. Part 2 (Dose Expansion), Cycle 1/Day 15

The following procedures will be completed pre-dose during the Part 2, Cycle 1/Day 15 visit:

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain a blood sample for PK measurements.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer quizartinib per protocol.

Administer milademetan per protocol if subject is in the qd 3/14 × 2 dosing schedule.

The following procedures will be completed post-dose during the Part 2, Cycle 1/Day 15 visit:

Perform a 12-lead ECG in triplicate at 3 hours post-dose as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain a blood sample for PK measurements at 3 hours post-dose as indicated in Section 8.

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense milademetan per protocol if subject is in the qd 3/14 × 2 dosing schedule.

6.3.2.6. Part 2 (Dose Expansion), Cycle 1/Day 22

The following procedures will be completed pre-dose during the Part 2, Cycle 1/Day 22 visit (± 2 days):

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Obtain a blood sample for PK measurements.

Obtain a blood sample for serum MIC-1 analysis.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer quizartinib per protocol.

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense and review pill diary (for at-home dosing, if regionally required) and assess treatment compliance.

The following procedures will be completed post-dose during the Part 2, Cycle 1/Day 22 visit:

Perform a 12-lead ECG in triplicate at 3 hours post-dose as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain a blood sample for PK measurements at 3 hours post-dose as indicated in Section 8.

6.3.2.7. Part 2 (Dose Expansion), Cycle 2/Day 1

The following procedures will be completed pre-dose during the Part 2, Cycle 2/Day 1 visit (± 2 days):

Perform a complete physical examination and record weight.

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Assess functional status using the ECOG Performance Status Scale.

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Obtain a blood sample for PK measurements.

Obtain bone marrow biopsies/aspirates for disease assessment and biomarker tests.

- **Note:** Submission of bone marrow specimens is required for biomarker tests (see details in Section 7.1.1.1 and instructions in the Laboratory Manual). Additionally, submission of bone marrow samples for MRD analysis is required if <5% blasts in bone marrow is observed.

Obtain blood samples for exploratory biomarkers.

Obtain a blood sample for banking plasma.

Obtain a blood sample for serum MIC-1 analysis.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer milademetan per protocol.

Administer quizartinib per protocol.

Dispense milademetan per protocol (to take home, if regionally required).

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense and review pill diary (for at-home dosing, if regionally required) and assess treatment compliance.

The following procedures will be completed post-dose during the Part 2, Cycle 2/Day 1 visit:

Perform a 12-lead ECG in triplicate at 3 hours post-dose as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain a blood sample for PK measurements at 3 hours post-dose as indicated in Section 8.

6.3.2.8. Part 2 (Dose Expansion), Cycle 2/Days 8, 15, and 22

The following procedures will be completed pre-dose during the Part 2, Cycle 2/Days 8, 15, and 22 visits (± 2 days):

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Obtain a blood sample for PK measurements.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer milademetan per protocol on only Part 2, Cycle 2/Day 8 visit, or (if subject is in the qd 3/14 × 2 dosing schedule) on Part 2, Cycle 2/Day 15 visit.

Administer quizartinib per protocol.

Dispense milademetan per protocol (to take home, if regionally required) on only Part 2, Cycle 2/Day 8 visit, or (if subject is in the qd 3/14 × 2 dosing schedule) on Part 2, Cycle 2/Day 15 visit.

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense and review pill diary (for at-home dosing, if regionally required) and assess treatment compliance.

The following procedures will be completed post-dose during the Part 2, Cycle 2/Days 8, 15, and 22 visits:

Perform a 12-lead ECG in triplicate at 3 hours post-dose as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain a blood sample for PK measurements at 3 hours post-dose as indicated in Section 8.

6.3.2.9. Part 2 (Dose Expansion), Cycle 3/Day 1

The following procedures will be completed pre-dose during the Part 2, Cycle 3/Day 1 visit (± 4 days):

Perform a complete physical examination and record weight.

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Assess functional status using the ECOG Performance Status Scale.

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Obtain a serum sample for pregnancy testing in women of childbearing potential.

Obtain a blood sample for PK measurements.

Obtain bone marrow biopsies/aspirates for disease assessment and biomarker tests.

- **Note:** Submission of bone marrow specimens is required for biomarker tests (see details in Section 7.1.1.1 and instructions in the Laboratory Manual). Additionally, submission of bone marrow samples for MRD analysis is required if <5% blasts in bone marrow is observed.

Obtain blood samples for exploratory biomarkers.

Obtain a blood sample for banking plasma.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer milademetan per protocol.

Administer quizartinib per protocol.

Dispense milademetan per protocol (to take home, if regionally required).

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense and review pill diary (for at-home dosing, if regionally required) and assess treatment compliance.

The following procedures will be completed post-dose during the Part 2, Cycle 3/Day 1 visit:

Perform a 12-lead ECG in triplicate at 3 hours post-dose as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain a blood sample for PK measurements at 3 hours post-dose as indicated in Section 8.

6.3.2.10. Part 2 (Dose Expansion), Cycle 3/Days 8, 15, and 22

The following procedures will be completed pre-dose during the Part 2, Cycle 3/Days 8, 15, and 22 visits (± 4 days):

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Obtain a blood sample for PK measurements.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer milademetan per protocol on only Part 2, Cycle 3/Day 8 visit, or (if subject is in the qd 3/14 × 2 dosing schedule) on Part 2, Cycle 3/Day 15 visit.

Administer quizartinib per protocol.

Dispense milademetan per protocol (to take home, if regionally required) on only Part 2, Cycle 3/Day 8 visit, or (if subject is in the qd 3/14 × 2 dosing schedule) on Part 2, Cycle 3/Day 15 visit.

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense and review pill diary (for at-home dosing, if regionally required) and assess treatment compliance.

The following procedures will be completed post-dose during the Part 2, Cycle 3/Days 8, 15, and 22 visits:

Perform a 12-lead ECG in triplicate at 3 hours post-dose as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain a blood sample for PK measurements at 3 hours post-dose as indicated in Section 8.

6.3.2.11. Part 2 (Dose Expansion), Day 1 of Cycle 4 and All Subsequent Cycles

The following procedures will be performed pre-dose during the Part 2, Cycle 4/Day 1 visit (± 4 days), and all subsequent cycles on Day 1 visits (± 4 days):

Perform a complete physical examination and record weight.

Perform a 12-lead ECG in triplicate up to Part 2, Cycle 6/Day 1 after subject has been in supine position for 5 minutes prior.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Assess functional status using the ECOG Performance Status Scale.

Obtain blood samples for safety laboratory tests (hematology and serum chemistry). In subjects who develop GI AEs, such as v–’ ≥η≥,,z(t ,,w(w≥t Δ≤xt (–y(S Δt wx(2, blood chemistry and 12-lead ECGs will be assessed weekly or more frequently as clinically needed until the GI AEs and electrolyte abnormt ”≥η≥xβ(t Δx(Δxβ–” xw(η–(S Δt wx(1. In subjects with potassium, calcium, a,,w(’ t z,,xβ≥π’ (S Δt wx(1, blood chemistry and 12-lead ECGs will be assessed twice a week.

Obtain a serum sample for pregnancy testing in women of childbearing potential on Day 1 of every 3 cycles from Cycle 3 (ie, Cycles 6, 9, 12, etc).

Obtain a blood sample for PK measurements up to Part 2, Cycle 6/Day 1.

Obtain bone marrow biopsies/aspirates for disease assessment and biomarker tests (see details in Section 7.1.1 and instructions in the Laboratory Manual):

If subject achieves CR, CRi, or MLFS before Cycle 4/Day 1 (eg, CR on Cycle 3/Day 1), then bone marrow biopsies/aspirates will be not required on Cycle 4/Day 1.

- Perform bone marrow biopsies/aspirates on Day 1 of Cycles 6, 9, and 12 if subject remains in CR, CRi, or MLFS.
- If subject remains in CR, CRi, or MLFS on Cycle 12/Day 1, bone marrow biopsies/aspirates will be required at Day 1 of Cycles 18, 24, and every 6 cycles thereafter.

If subject does not achieve CR, CRi, or MLFS before Cycle 4/Day 1(eg, PR on Cycle 3/Day 1), then bone marrow biopsies/aspirates will be required on Cycle 4/Day 1 and on Day 1 of every cycle thereafter until subject achieves CR, CRi, or MLFS.

Unscheduled bone marrow biopsies/aspirates can be performed whenever clinically indicated.

Note: Submission of bone marrow specimens beyond Cycle 3/Day 1 is required at the following visits (see details in Section 7.1.1.1 and instructions in the Laboratory Manual):

Bone marrow samples on Day 1 of Cycles 6, 9, 12, 18, 24, and every 6 cycles thereafter.

Bone marrow sample from unscheduled bone marrow biopsies/aspirates when disease progression (relapse or progressive disease) is suspected.

Additionally, submission of bone marrow samples for MRD analysis (eg, flow cytometry and/or next generation sequencing) is required on the day when <5% blasts in bone marrow is observed and/or at the subsequent timepoints for bone marrow sample collection.

Bone marrow samples from other timepoints are not required to be submitted (eg, Cycle 4/Day1).

Obtain blood samples for exploratory biomarkers. Sample for biomarker assessment is every 3 cycles after Cycle 3.

Obtain a blood sample for banking plasma (every 3 cycles after Cycle 2).

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer milademetan per protocol.

Administer quizartinib per protocol.

Dispense milademetan per protocol (to take home, if regionally required).

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense and review pill diary (for at-home dosing, if regionally required) and assess treatment compliance.

The following procedures will be completed post-dose during the Part 2, Cycles 4 to 6 on Day 1:

Perform a 12-lead ECG in triplicate at 3 hours post-dose up to Part 2, Cycle 6/Day 1 as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain a blood sample for PK measurements at 3 hours post-dose up to Part 2, Cycle 6/Day 1 as indicated in Section 8.

6.3.3. Treatment Period, Part 2 (Dose Expansion), Subjects in the DDI Substudy

Unless otherwise stated, an activity occurs before study drug administration.

6.3.3.1. Part 2 (Dose Expansion DDI Substudy), Pre-cycle/Day −2

The following procedures will be completed during the Part 2 DDI substudy, Pre-cycle/Day ; visit:

Perform a complete physical examination and record weight.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Assess functional status using the ECOG Performance Status Scale.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Perform a 12-lead ECG in triplicate at 0, 1, 2, 4, and 6 hours approximately time-matched with Day 1 measurements as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

6.3.3.2. Part 2 (Dose Expansion DDI Substudy), Cycle 1/Day −1

The following procedures will be completed pre-dose during the Part 2 DDI substudy, Cycle 1/Day 1 visit. If the Screening visit for Part 2 is completed within 72 hours of Cycle 1/Day 1, blood samples for safety laboratory tests need not be collected. Study medication will be administered on an empty stomach (no food for at least 2 hours pre-dose):

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain a blood sample for PK measurements.

Obtain a blood sample for serum MIC-1 analysis.

Obtain a blood sample for banking plasma.

Obtain blood samples for exploratory biomarkers.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Obtain a buccal swab or saliva for PGx.

Informed consent specifically allowing PGx testing sample storage must be obtained before collecting sample.

Administer milademetan per protocol.

Subjects must fast for 2 hours post-dose.

The following procedures will be completed post-dose during the Part 2 DDI substudy, Cycle 1/Day 1 visit:

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) at 3 hours (± 10 minutes) post-dose.

Perform a 12-lead ECG in triplicate at 1, 2, 4, and 6 hours post-dose as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain blood samples for PK measurements at the following timepoints: 0.5, 1, 2, 3, 4, 6, and 8 hours post-dose as indicated in Section 8. Blood samples should be collected within 10 minutes after corresponding ECG measurements.

6.3.3.3. Part 2 (Dose Expansion DDI Substudy), Cycle 1/Day 1

The following procedures will be completed pre-dose during the Part 2 DDI substudy, Cycle 1/Day 1 visit. If the safety assessments were completed on Cycle 1/Day 1, they need not be repeated for Cycle 1/Day 1, except for PK and ECGs and vital signs.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain a blood sample for PK measurements.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer milademetan per protocol.

Administer quizartinib per protocol.

The following procedures will be completed post-dose during the Part 2 DDI substudy, Cycle 1/Day 1 visit:

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) at 3 hours (± 10 minutes) post-dose.

Perform a 12-lead ECG in triplicate at 3 hours post-dose as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain a blood sample for PK measurements at 3 hours post-dose as indicated in Section 8.

6.3.3.4. Part 2 (Dose Expansion DDI Substudy), Cycle 1/Day 2

The following procedures will be completed pre-dose during the Part 2 DDI substudy, Cycle 1/Day 2 visit:

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain a blood sample for PK measurements.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Obtain blood samples for exploratory biomarkers.

Obtain a blood sample for serum MIC-1 analysis.

Administer milademetan per protocol.

Administer quizartinib per protocol.

Dispense milademetan per protocol (to take home, if regionally required).

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense a pill diary with dose administration instructions (for at-home dosing, if regionally required).

6.3.3.5. Part 2 (Dose Expansion DDI Substudy), Cycle 1/Day 8

The following procedures will be completed pre-dose during the Part 2 DDI substudy, Cycle 1/Day 8 visit (± 2 days):

Perform a complete physical examination and record weight.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Assess functional status using the ECOG Performance Status Scale.

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain a blood sample for PK measurements.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Obtain blood samples for exploratory biomarkers.

Obtain a blood sample for serum MIC-1 analysis.

Obtain a blood sample for banking plasma.

Administer milademetan per protocol.

Administer quizartinib per protocol.

Dispense milademetan per protocol (to take home, if regionally required).

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense and review pill diary (for at-home dosing, if regionally required) and assess treatment compliance.

6.3.3.6. Part 2 (Dose Expansion DDI Substudy), Cycle 1/Day 14

The following procedures will be completed pre-dose during the Part 2 DDI substudy, Cycle 1/Day 14 visit (± 2 days):

Perform a complete physical examination and record weight.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Assess functional status using the ECOG Performance Status Scale.

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain a blood sample for PK measurements.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Obtain a blood sample for serum MIC-1 analysis.

Administer milademetan per protocol.

Administer quizartinib per protocol.

Dispense and review pill diary (for at-home dosing, if regionally required) and assess treatment compliance.

The following procedures will be completed post-dose during the Part 2, Cycle 1/Day 14 visit:

Perform a 12-lead ECG in triplicate at 3 hours post-dose as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain a blood sample for PK measurements at 3 hours post-dose as indicated in Section 8.

6.3.3.7. Part 2 (Dose Expansion DDI Substudy), Cycle 1/Day 15

The following procedures will be completed pre-dose during the Part 2, Cycle 1/Day 15 visit:

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain a blood sample for PK measurements.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer quizartinib per protocol.

The following procedures will be completed post-dose during the Part 2, Cycle 1/Day 15 visit:

Perform a 12-lead ECG in triplicate at 3 hours post-dose as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain a blood sample for PK measurements at 3 hours post-dose as indicated in Section 8.

Dispense quizartinib per protocol (to take home, if regionally required).

6.3.3.8. Part 2 (Dose Expansion DDI Substudy), Cycle 1/Day 22

The following procedures will be completed pre-dose during the Part 2 DDI substudy, Cycle 1/Day 22 visit (± 2 days):

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain a blood sample for PK measurements.

Obtain a blood sample for serum MIC-1 analysis.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer quizartinib per protocol.

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense and review pill diary (for at-home dosing, if regionally required) and assess treatment compliance.

The following procedures will be completed post-dose during the Part 2, Cycle 1/Day 22 visit:

Perform a 12-lead ECG in triplicate at 3 hours post-dose as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain a blood sample for PK measurements at 3 hours post-dose.

6.3.3.9. Part 2 (Dose Expansion DDI Substudy), Cycle 1/Day 28

The following procedures will be completed pre-dose during the Part 2 DDI substudy, Cycle 1/Day 28 visit. Study medication will be administered on an empty stomach (no food for at least 2 hours pre-dose):

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain a blood sample for PK measurements.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer quizartinib per protocol.

Subjects must fast for 2 hours post-dose.

Dispense and review pill diary and assess treatment compliance.

The following procedures will be completed post-dose during the Part 2 DDI substudy, Cycle 1/Day 28 visit:

Perform a 12-lead ECG in triplicate at 1, 2, 4, and 6 hours post-dose as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain a blood sample for PK measurements at the following timepoints: 0.5, 1, 2, 3, 4, 6, and 8 hours post-dose as indicated in Section 8.

6.3.3.10. Part 2 (Dose Expansion DDI Substudy), Cycle 2/Day 1

The following procedures will be completed pre-dose during the Part 2 DDI substudy, Cycle 2/Day 1 visit. Study medication will be administered on an empty stomach (no food for at least 2 hours pre-dose):

Perform a complete physical examination and record weight.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Assess functional status using the ECOG Performance Status Scale.

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain a blood sample for PK measurements.

Obtain bone marrow biopsies/aspirates for disease assessment and biomarker tests.

Note: Submission of bone marrow specimens is required for biomarker tests (see details in Section 7.1.1.1 and instructions in the Laboratory Manual). Additionally, submission of bone marrow samples for MRD analysis is required if <5% blasts in bone marrow is observed.

Obtain blood samples for exploratory biomarkers.

Obtain a blood sample for serum MIC-1 analysis.

Obtain a blood sample for banking plasma.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer milademetan per protocol.

Administer quizartinib per protocol.

Subjects must fast for 2 hours post-dose of both study drugs.

The following procedures will be completed post-dose during the Part 2 DDI substudy, Cycle 2/Day 1 visit:

Perform a 12-lead ECG in triplicate at 1, 2, 4, and 6 hours post-dose as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain a blood sample for PK measurements at the following timepoints: 0.5, 1, 2, 3, 4, 6, and 8 hours post-dose as indicated in Section 8.

6.3.3.11. Part 2 (Dose Expansion DDI Substudy), Cycle 2/Day 2

The following procedures will be completed pre-dose during the Part 2 DDI substudy, Cycle 2/Day 2 visits:

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain blood samples for PK measurements.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer milademetan per protocol.

Administer quizartinib per protocol.

Dispense milademetan per protocol (to take home, if regionally required).

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense/review pill diary (for at-home dosing, if regionally required).

6.3.3.12. Part 2 (Dose Expansion DDI Substudy), Cycle 2/Day 8

The following procedures will be completed pre-dose during the Part 2 DDI substudy, Cycle 2/Day 8 visits (± 2 days):

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain blood samples for PK measurements.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer milademetan per protocol.

Administer quizartinib per protocol.

Dispense milademetan per protocol (to take home, if regionally required).

Dispense quizartinib per protocol (to take home, if regionally required).

Review pill diary and assess treatment compliance (for at-home dosing, if regionally required).

6.3.3.13. Part 2 (Dose Expansion DDI Substudy), Cycle 2/Day 14

The following procedures will be completed pre-dose during the Part 2 DDI substudy, Cycle 2/Day 14 visit. Study medication will be administered on an empty stomach (no food for at least 2 hours pre-dose):

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain a blood sample for PK measurements.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer milademetan per protocol.

Administer quizartinib per protocol.

Subjects must fast for 2 hours post-dose of both study drugs.

Review and dispense pill diary (for at-home dosing, if regionally required) and assess treatment compliance.

The following procedures will be completed post-dose during the Part 2 DDI substudy, Cycle 2/Day 14 visit:

Perform a 12-lead ECG in triplicate at 1, 2, 4, and 6 hours post-dose as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain a blood sample for PK measurements at the following timepoints: 0.5, 1, 2, 3, 4, 6, and 8 hours post-dose as indicated in Section 8.

6.3.3.14. Part 2 (Dose Expansion DDI Substudy), Cycle 2/Day 15

The following procedures will be completed pre-dose during the Part 2 DDI substudy, Cycle 2/Day 15 visit:

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Obtain a blood sample for PK measurements.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer quizartinib per protocol.

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense pill diary and assess treatment compliance (for at-home dosing, if regionally required).

6.3.3.15. Part 2 (Dose Expansion DDI Substudy), Cycle 2/Day 22

The following procedures will be completed pre-dose during the Part 2 DDI substudy, Cycle 2/Day 22 visit (± 2 days):

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Obtain a blood sample for PK measurements.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer quizartinib per protocol.

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense pill diary and assess treatment compliance (for at-home dosing, if regionally required).

6.3.3.16. Part 2 (Dose Expansion DDI Substudy), Cycle 3/Day 1

The following procedures will be completed pre-dose during the Part 2 DDI substudy, Cycle 3/Day 1 visit (± 4 days):

Perform a complete physical examination and record weight.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Assess functional status using the ECOG Performance Status Scale.

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Obtain a serum sample for pregnancy testing in women of childbearing potential.

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain a blood sample for PK measurements.

Obtain bone marrow biopsies/aspirates for disease assessment and biomarker tests.

Note: Submission of bone marrow specimens is required for biomarker tests (see details in Section 7.1.1.1 and instructions in the Laboratory Manual). Additionally, submission of bone marrow samples for MRD analysis is required if <5% blasts in bone marrow is observed.

Obtain blood samples for exploratory biomarkers.

Obtain a blood sample for banking plasma.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer milademetan per protocol.

Administer quizartinib per protocol.

Dispense milademetan per protocol (to take home, if regionally required).

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense and review pill diary (for at-home dosing, if regionally required) and assess treatment compliance.

The following procedures will be completed post-dose during the Part 2, Cycle 3/Day 1:

Perform a 12-lead ECG in triplicate at 3 hours post-dose as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain a blood sample for PK measurements at 3 hours post-dose as indicated in Section 8.

6.3.3.17. Part 2 (Dose Expansion DDI Substudy), Cycle 3/Days 8, 15, and 22

The following procedures will be completed pre-dose during the Part 2 DDI substudy, Cycle 3/Days 8, 15, and 22 visits:

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Obtain blood samples for safety laboratory tests (hematology and serum chemistry).

Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.

Obtain a blood sample for PK measurements.

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer milademetan per protocol on only Part 2, Cycle 3/Day 8 visit.

Administer quizartinib per protocol.

Dispense milademetan per protocol (to take home, if regionally required) on only Part 2, Cycle 3/Day 8 visit.

Dispense quizartinib per protocol (to take home, if regionally required).

Review and dispense pill diary (for at-home dosing, if regionally required) and assess treatment compliance.

6.3.3.18. Part 2 (Dose Expansion DDI Substudy), Day 1 of Cycle 4 and All Subsequent Cycles

The following procedures will be completed pre-dose during the Part 2 DDI substudy on Cycle 4/Day 1 (± 4 days) and all subsequent Cycles/Day 1 (± 4 days) visits:

Perform a complete physical examination and record weight.

Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).

Assess functional status using the ECOG Performance Status Scale.

Obtain blood samples for safety laboratory tests (hematology and serum chemistry). In subjects who develop GI AEs, such as v–’ ≥ŋ≥„z(t „„w(w≥t Δ≤xt (–y(S Δt wx(2, blood chemistry and 12-lead ECGs will be assessed weekly or more frequently as clinically needed until the GI AEs and electrolyte abnormt ”≥ŋ≥xβ(t Δx(Δxβ–” xw(ŋ–(S Δt wx(1. In subjects with potassium, vt ’v≥π’ 5(t „„w(’ t z„„xβ≥π’ (S Δt wx(1, blood chemistry and 12-lead ECGs will be assessed twice a week.

Obtain a serum sample for pregnancy testing in women of childbearing potential on Day 1 of every 3 cycles from Cycle 3 (ie, Cycles 6, 9, 12, etc).

Perform a 12-lead ECG in triplicate (up to Cycle 6/Day 1) after subject has been in supine position for 5 minutes prior.

Obtain blood samples for exploratory biomarkers. Sample for biomarker assessment is every 2 cycles after Cycle 2.

Obtain a blood sample for banking plasma (every 2 cycles after Cycle 4).

Obtain bone marrow biopsies/aspirates for disease assessment and biomarker tests (see details in Section 7.1.1 and instructions in the Laboratory Manual):

If subject achieves CR, CRi, or MLFS before Cycle 4/Day 1 (eg, CR on Cycle 3/Day 1), then bone marrow biopsies/aspirates will be not required on Cycle 4/Day 1.

- Perform bone marrow biopsies/aspirates on Day 1 of Cycles 6, 9, and 12 if subject remains in CR, CRi, or MLFS.
- If subject remains in CR, CRi, or MLFS on Cycle 12/Day 1, bone marrow biopsies/aspirates will be required at Day 1 of Cycles 18, 24, and every 6 cycles thereafter.

If subject does not achieve CR, CRi, or MLFS before Cycle 4/Day 1(eg, PR on Cycle 3/Day 1), then bone marrow biopsies/aspirates will be required on Cycle 4/Day 1 and on Day 1 of every cycle thereafter until subject achieves CR, CRi, or MLFS.

Unscheduled bone marrow biopsies/aspirates can be performed whenever clinically indicated.

Note: Submission of bone marrow specimens beyond Cycle 3/Day 1 is required at the following visits (see details in Section 7.1.1.1 and instructions in the Laboratory Manual):

Bone marrow samples on Day 1 of Cycles 6, 9, 12, 18, 24, and every 6 cycles thereafter.

Bone marrow sample from unscheduled bone marrow biopsies/aspirates when disease progression (relapse or progressive disease) is suspected.

Additionally, submission of bone marrow samples for MRD analysis (eg, flow cytometry and/or next generation sequencing) is required on the day when <5% blasts in bone marrow is observed and/or at the subsequent timepoints for bone marrow sample collection.

Bone marrow samples from other timepoints are not required to be submitted (eg, Cycle 4/Day1).

Obtain a blood sample for PK measurements (up to Cycle 6/Day 1).

Record concomitant medications.

Record transfusion (RBC, platelet, other).

Assess subjects for AEs.

Administer milademetan per protocol.

Administer quizartinib per protocol.

Dispense milademetan per protocol (to take home, if regionally required).

Dispense quizartinib per protocol (to take home, if regionally required).

Dispense and review pill diary (for at-home dosing, if regionally required) and assess treatment compliance.

The following procedures will be completed post-dose during the Part 2, Cycle 4/Day 1, and up to Part 2, Cycle 6 on Day 1 visits:

Perform a 12-lead ECG in triplicate at 3 hours post-dose as indicated in ECG manual. Subject should be in supine position for 5 minutes prior to each reading.

Obtain a blood sample for PK measurements at 3 hours post-dose as indicated in Section 8.

6.4. End-of-Treatment - Part 1 and Part 2 (Post-cycle)

The End-of-treatment visit should occur at the earliest day possible within 30 days after the last administration of study drug(s), but before beginning any other form of anticancer therapy.

The following assessments will be performed at this visit:

- b uɳ ≥,(v–„y≥Δ' t ɳ≥„(–y(βπu–xvη β(v–„βx„ɳ(ɳ–(ux≥,z(v–„ɳ vɳxw(y–Δ(y–"'– -up phase (Section 6.5).
- Perform a complete physical examination and record weight and height.
- Obtain vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).
- Assess functional status using the ECOG Performance Status Scale.
- Obtain blood samples for safety laboratory tests (hematology and serum chemistry).
- Obtain a serum sample for pregnancy testing in women of childbearing potential.
- Perform a 12-lead ECG in triplicate after subject has been in supine position for 5 minutes prior.
- Obtain a blood sample for PK measurements.
- Obtain blood samples for exploratory biomarkers.
- Obtain a blood sample for banking plasma.
- Obtain blood for biomarkers from subjects who achieved an initial CR, CRi, MLFS, or PR but later relapsed (after CR or CRi) or developed PD (after MLFS or PR) while on therapy.
- Record concomitant medications.
- Assess subjects for AEs.
- Review pill diary and assess treatment compliance.
- Record reason for treatment discontinuation.
- Bone marrow re-biopsy and/or aspirate for subjects who achieved an initial CR, CRi, MLFS, or PR but later relapsed (after CR or CRi) or developed PD (after MLFS or PR) while on therapy (See Section 6.4.1).

6.4.1. End-of-Treatment Bone Marrow Re-biopsy/Aspirate (Part 1 and Part 2)

To search for possible mechanisms of acquired resistance to milademetan and quizartinib combination, a bone marrow re-biopsy or aspirate will be performed in subjects who have achieved an initial CR, CRi, MLFS, or PR but later relapse (after CR or CRi) or develop PD (after MLFS or PR) while on therapy. Bone marrow re-biopsy or aspirate would be performed within 30 days following the last dose of study drugs, prior to initiating subsequent AML therapy.

6.5. Follow-up Phase – Part 1 and Part 2

All subjects who discontinued study treatment will enter the Follow-up Phase and will undergo the following assessments. Subjects discontinued from study treatment because of withdrawal of consent for follow-up are exempted.

6.5.1. Follow-up 30 Days After End-of-treatment

The 30-day Follow-up visit should occur 30 (± 5) days after the last administration of study drug(s). Follow-up information will be collected via a phone call or site visit. The Investigator should follow subjects with AEs until the event has resolved or the condition has stabilized. In case of unresolved AEs, including significant abnormal laboratory values at the End-of-treatment assessment, these events will be followed up until resolution or until they become clinically not relevant.

The following information will be collected at the 30-day Follow-up visit:

Assessment of AEs.

Current medications.

Subject survival status.

Date and cause of death, if applicable

Subsequent AML therapy.

HCT and HCT-relevant information, if performed.

6.5.2. Long-term Survival Follow-up

The Long-term Survival Follow-ups should occur every 3 months (± 2 weeks) after the first 30-day Follow-up visit until subject death or until the Sponsor terminates the study. Additionally, the most updated survival follow-up status may be collected when the Sponsor performs survival analysis (for example, asking for survival status again when a subject had survival follow-up 2 months prior).

The following information will be collected, if feasible:

Subject survival status.

Date and cause of death, if applicable.

Subsequent AML therapy.

HCT and HCT-relevant information, if performed.

If direct contacts are not possible or if Long-term Survival Follow-up is not performed due to withdrawal of consent, subject refusal to participate in long-term follow-up, or loss to follow-up, the site must make every effort to collect survival status from public records (eg, death certificates) in accordance with local laws and document as best possible the specific reason for inability to collect long-term follow-up data.

7. EFFICACY ASSESSMENTS

7.1. Assessments for Efficacy Endpoint(s)

Efficacy assessments will be based on U, xβ›žzt η−Δβ (evaluations of bone marrow, peripheral and physical examination or pathological diagnosis of extramedullary disease at Screening and at protocol-defined timepoints (eg, Cycle 2/Day 1, etc) while the subject remains on study drug. The clinical activity of the treatment will be assessed using 2017 ELN recommendations.[19] The percentage of subjects undergoing allogeneic HCT directly following protocol-specified treatment with no intervening AML therapy and transfusion independence is based on I,, xβ›žzt η−Δβ (Δx×−Δβ7((The response criteria are defined in Section 17.4 and Section 17.5. The efficacy endpoints are listed in Section 2.4.3.

7.1.1. Bone Marrow Biopsies/Aspirates

An overview of the schedule for bone marrow biopsies/aspirates is presented in Figure 7.1.

During the first 12 cycles (first year):

Bone marrow biopsies/aspirates are mandated on Day 1 of Cycles 2 and 3 for all subjects.

If subject achieves CR, CRi, or MLFS before Cycle 4/Day 1 (eg, CR on Cycle 3/Day 1), then bone marrow biopsies/aspirates will not be required on Cycle 4/Day 1.

- Perform bone marrow biopsies/aspirates on Day 1 of Cycles 6, 9, and 12 if subject remains in CR, CRi, or MLFS.

If subject does not achieve CR, CRi, or MLFS before Cycle 4/Day 1 (eg, PR on Cycle 3/Day 1), then bone marrow biopsies/aspirates will be required on Cycle 4/Day 1 and on Day 1 of every cycle thereafter until subject achieves CR, CRi, or MLFS.

Beyond Cycle 4/Day 1, for subjects who achieve first CR, CRi, or MLFS, perform bone marrow biopsies/aspirates on Day 1 of Cycles 6, 9, and 12. For example:

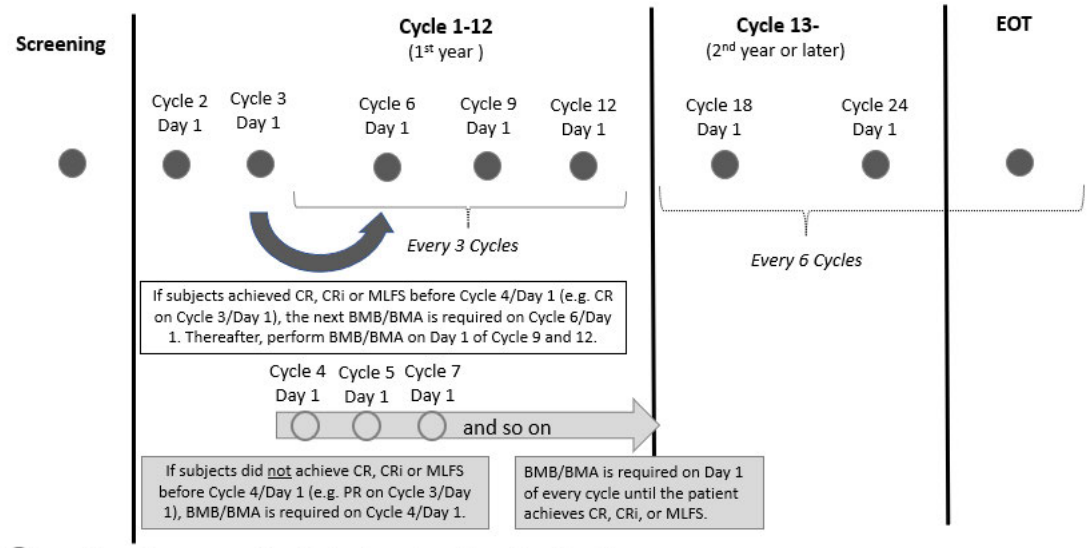
- If subject achieves first CRi (without prior MLFS) on Cycle 5/Day 1, perform next bone marrow biopsies/aspirates on Cycle 6/Day 1.
- If subject achieves first CR (without prior CRi or MLFS) on Cycle 7/Day 1, perform next bone marrow biopsies/aspirates on Cycle 9/Day 1.

Beyond 12 cycle (second year or later):

If subject remains in CR, CRi, or MLFS on Cycle 12/Day 1, bone marrow biopsies/aspirates will be required on Day 1 of Cycles 18, 24, and every 6 cycles thereafter.

Unscheduled bone marrow biopsies/aspirates can be performed whenever clinically indicated. All unscheduled bone marrow assessments performed on non-visit days must be reported as unscheduled visits.

Figure 7.1: Schedule for Bone Marrow Biopsies/Aspirates



Mandatory bone marrow biopsies/aspirates (BMB/BMA) for All Subjects
⇒ BM sample submission is required for translational research for these timepoints. Additionally, submission of BM samples for minimal residual disease analysis (e.g. flow cytometry, or next generation sequencing) is required on the day when <5% blasts in BM is observed, and/or at the subsequent timepoints for BM sample collection.

BMB/BMA required only when subjects did not achieve CR, CRi or MLFS
⇒ BM sample submission is not required unless disease progression (relapse or progressive disease) is suspected.

BM = bone marrow; BMA = bone marrow aspirate; BMB = bone marrow biopsy; CR = complete remission; CRi = CR with incomplete blood count recovery; EOT = end of treatment; MLFS = morphologic leukemia-free state; PR = partial remission

7.1.1.1. Bone Marrow Samples for Translational Research

Bone marrow samples for translational research must be submitted at the following visits:

- Bone marrow samples at Screening and on Day 1 of Cycles 2, 3, 6, 9, 12, 18, 24, and every 6 cycles thereafter.
- Bone marrow sample from unscheduled bone marrow biopsies/aspirates when disease progression (relapse or progressive disease) is suspected.
- Additionally, submission of bone marrow samples for MRD analysis (eg, flow cytometry and/or next generation sequencing) is required on the day when <5% blasts in bone marrow is observed and/or at the subsequent timepoints for bone marrow sample collection.

Bone marrow samples from other timepoints are not required to be submitted (eg, Cycle 4/Day1).

Please refer to the Laboratory Manual for additional details and instructions.

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

8.1. Pharmacokinetic (PK) Assessment(s)

In Part 1, blood samples will be collected for the measurement of plasma concentrations of milademetan, quizartinib and AC886 as shown in Table 8.1. The PK parameters (Cmax and AUC24h) will be estimated by non-compartmental analysis. In addition, blood concentrations of quizartinib and AC886 may also be evaluated.

Table 8.1: Intensive PK Sampling (Part 1)

Cycle 1								
	Day 1							
Hour Post-dose	Pre-dose[a]	0.5[b]	1[b]	2[b]	3[b]	4[c]	6-8[d]	24[c,e]
	Day 14							
Hour Post-dose	Pre-dose[a]	0.5[b]	1[b]	2[b]	3[b]	4[c]	6-8[d]	24[c,e]

[a] Within 1 hour prior to drug administration.
[b] ± 10 min
[c] ± 15 min
[d] PK sample will be collected between time window of 6 to 8 hours post-dose. Actual time of sample collection must be recorded.
[e] The 24-hour timepoint will be collected as pre-dose of the visit on the following day.
Note: For PK samples corresponding to ECG measurements, blood samples should be collected within 10 minutes after ECG measurements.

In Part 2 (except subjects in the DDI substudy), sparse PK samples for plasma concentrations of milademetan, quizartinib, and AC886 will be collected as shown in Table 8.2. Please see Section 9.9 for details of PK time-matched ECG collection. Blood should be collected within 10 minutes after ECG measurement.

Table 8.2: Sparse PK Sampling (Part 2)

	Cycle 1/Days 1, 8, 14, 15,[c] and 22[c]	
Hour Post-dose	Pre-dose [a,b]	3[b]
	Cycles 2 to 3/Days 1, 8, 15,[c] and 22[c]	
Hour Post-dose	Pre-dose[a,b]	3[b]
	Cycles 4 to 6/Day 1	
Hour Post-dose	Pre-dose[a,b]	3[b]

[a] Within 1 hour prior to drug administration.
[b] ± 10 min.
[c] Measurement of quizartinib and AC886 only.
Note: For PK samples corresponding to ECG measurements, blood samples should be collected within 10 minutes after ECG measurements.

The effect of quizartinib on milademetan PK and the effect of milademetan on quizartinib PK will be studied in a subset of 12 subjects in the dose expansion cohorts. In this substudy, concomitant administration of strong CYP3A inhibitors will be prohibited for the first 2 cycles of

treatment. The substudy will include administration of milademetan alone on Cycle 1/Day 1 only, quizartinib administered alone (Days 15 to 28) of each cycle and concomitant administration of quizartinib and milademetan (Days 1 to 14) of each cycle as shown in Figure 8.1. Pharmacokinetic samples will be collected as shown in Table 8.3. The PK parameters (Cmax and AUC24h) for milademetan, quizartinib, and AC886 will be assessed to evaluate the effects of (1) steady-state quizartinib on single dose milademetan PK and (2) repeated doses of milademetan on steady-state PK of quizartinib and AC886. The effect of quizartinib on milademetan will be assessed by the comparison of Treatment A: milademetan single dose (C1D :) to Treatment C: milademetan single dose + quizartinib multiple dose (C2D1). The effect of milademetan on quizartinib will be assessed by the comparison of Treatment B: quizartinib multiple dose (C1D28) to Treatment D: quizartinib multiple dose + milademetan multiple dose (C2D14). ECGs will be measured at approximately the same time each day starting at Day ; to capture the circadian rhythm in ECG for an estimate of time-' t ηv≤xw(v≤t ,,zx(yΔ–' (ut βx'≥,x(≥,(d g vR(1 d g vR27(g≤e timepoints for ECG measurements are at pre-dose (or Hour 0), 1, 2, 4 and 6 hours post-dose.

Figure 8.1: PK Substudy Design (Part 2) with Milademetan QD 14/28 Schedule

Cycle 1					**Cycle 2**	
Day -2	**Day -1**	**Day 1**	**Day 14**	**Day 28**	**Day 1**	**Day 14**
	DS-3032 PK				DS-3032 PK	DS-3032 PK
				Quizartinib PK	Quizartinib PK	Quizartinib PK
ECG	ECG			ECG	ECG	ECG
	DS-3032b dose: QD x 14d				DS-3032b dose: QD x 14 d	
		Quizartinib dose: QD x 28d			Quizartinib dose: QD x 28d	

PK= pharmacokinetics, QD = once daily.

Table 8.3: PK Substudy Timepoints

Cycle 1									
	Day 1 (milademetan only)								
Hour Post-dose	Pre-dose[a]	0.5[b]	1[b]	2[b]	3[b]	4[c]	6[c]	8[c]	24[c]
	Day 28 (quizartinib, AC886)								
Hour Post-dose	Pre-dose[a]	0.5[b]	1[b]	2[b]	3[b]	4[c]	6[c]	8[c]	24[c]
Cycle 2									
	Day 1 (milademetan, quizartinib, AC886)								
Hour Post-dose	Pre-dose[a]	0.5[b]	1[b]	2[b]	3[b]	4[c]	6[c]	8[c]	24[c]
	Day 14 (milademetan, quizartinib, AC886)								
Hour Post-dose	Pre-dose[a]	0.5[b]	1[b]	2[b]	3[b]	4[c]	6[c]	8[c]	24[c]

[a] Within 1 hour prior to drug administration.
[b] ± 5 min.
[c] ± 10 min.
For PK samples corresponding to ECG measurements, blood samples should be collected within 10 min after ECG measurement.

See Section 9.9 for details of PK time-matched ECG collection. Blood should be collected within 10 minutes after ECG measurement.

8.2. Biomarkers

In this study, exploratory biomarker analyses will be used to investigate the effect of the quizartinib and milademetan at the molecular and cellular level to determine how changes in the markers may relate to exposure and clinical outcomes. Detailed instructions for the collection, handling, shipping and storage of biomarker samples are outlined in the Laboratory Manual.

8.2.1. Pharmacodynamic Assessment(s)

Pharmacodynamic assessments may include but are not limited to exploratory analysis of changes in LSC numbers, FLT3 signaled STAT5 downstream gene expression (eg, Mcl-1, Bcl2, c-Myc), and p53 downstream targets (eg, MDM2, MIC-1, PUMA, NOXA, Bax, CXCL12) in bone marrow AML or peripheral blood blasts and/or non-leukemic cells by analyzing RNA and/or proteins. Blood samples will be collected to monitor the changes in expression of pharmacodynamic biomarkers such as MIC-1 (and others). In subjects experiencing reduction of blasts in bone marrow to <5%, MRD may be monitored. In addition, mutations in TP53, FLT3, or other genes that may be present at baseline and occur during the course of treatment and/or at remission may be analyzed in bone marrow, peripheral blood, or circulating tumor DNA as exploratory evaluations.

8.2.2. Biomarkers for Subject Selection

Subjects with a known record of FLT3-ITD mutant AML based on local testing can enroll in the study and start to receive the treatment. However, the FLT3 status will be tested again in a central laboratory for confirmation of FLT3-ITD mutation. If the FLT3-ITD mutation is not detected in the centralized testing, the Investigator will discuss the results with the subject and the subject can decide to continue the study if deriving clinical benefit, or choose to discontinue the study participation.

Several publications reported the mutual exclusivity between TP53 mutations and FLT3/ITD mutations in AML,[20,21,22] and thus most of FLT3-ITD mutant AML may be TP53 wild type. Therefore, confirmation of TP53 wild type status is not required prior to starting the study treatment.

TP53 genotypes will be analyzed retrospectively at the end of the study, to confirm the TP53 mutation status. In addition, the mutation status of other genes that are involved in disease and disease progression may be monitored. DNA isolated from non-malignant cells (including buccal swab or saliva samples) will be used as a control for these mutation analyses.

8.2.3. Additional Biomarker Assessments

During the study, in addition to the biomarkers specified above, exploratory research may be conducted on the AML samples. These studies would extend the search for other potential biomarkers related to the effects of quizartinib and milademetan on AML and/or the resistance to the treatment. This may include the development of ways to detect, monitor or treat AML. These additional investigations would be dependent upon clinical outcome, reagent, and sample availability. These biomarkers may be analyzed from various samples, including bone marrow or peripheral blood cells, and plasma or serum samples.

8.3. Immunogenicity

No specific immunogenicity testing has been planned for the study drugs.

8.4. Pharmacogenomic Analysis

As part of this study, a buccal swab or saliva sample will be banked for possible future PGx analysis in germline DNA. In addition, this DNA may be used as a control to understand the differences between germline and tumor DNA.

In all parts of the study, on Day 1 of Cycle 1 prior to study drug administration (Day 1 for the DDI substudy subjects), a buccal swab or saliva sample must be collected from subjects. This sample will be processed to isolate genomic DNA and analyzed only for genes suspected to contribute to the safety and efficacy of the study drugs (milademetan and quizartinib) or as control samples for the molecular analysis of the leukemic cells.

Results will provide information on how individuals metabolize and/or react to the study drug or help to identify subjects who are more likely or less likely to benefit from the study drug. The information may be useful in increasing the knowledge of differences among individuals in the way they metabolize the study drug, as well as helping in the development of new drugs or improvement of existing drugs.

Because emerging information regarding the safety and efficacy of milademetan and quizartinib may become available in the future, samples will be retained for possible future analysis. Samples will be retained until the DNA has been exhausted or until the Sponsor instructs the genotyping contractor to destroy the sample (in accordance with laboratory procedures). During the period of storage, the DNA sample will not be immortalized or sold to anyone. Subjects will have the right to withdraw consent to their participation in the clinical study and may request to have their unused PGx sample destroyed at any time.

To ensure subject confidentiality, sample tubes will be identified only by a barcode label. This barcode will be linkxw(η–(η≤x(βπu–xvηβ(identifier number.

Please refer to the Laboratory Manual for instructions for sample collection, preparation, handling, storage, and shipment.

9. SAFETY EVALUATION AND REPORTING

9.1. Adverse Event Collection and Reporting

All clinical AEs (see Section 9.2.1 for definitions) occurring after the subject signs the ICF and up to 30 (± 5) days after the last dose of study medication (ie, the follow-up period), whether observed by the Investigator or reported by the subject, will be recorded on the Adverse Event Case Report Form page. Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to informed consent will be recorded as part of medical history.

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

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

At each visit, the Investigator will determine whether any AEs have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 9.2. The Investigator β(t ββxββ’ x,,η(’ πβη(ux(v’xt Δ’ (w–vπ’ x,,ηxw(≥,(η≤x(β≥ηx β(β–πΔvx(documentation.

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

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the ICF) procedures or treatments requiring hospitalization for pre-existing conditions that do not worsen in severity should not be reported as SAEs (see Section 9.2.2 for definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE. Disease progression is a study endpoint and, consequently, should not be reported as an AE/SAE. However, when a subject dies from disease progression with no other immediate vt πβxβ5(w≥βxt βx(×Δ–zΔxββ≥–,, (β≤–π’d be reported as an SAE.

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

9.2. Adverse Event

9.2.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (International Conference on Harmonisation [ICH] E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, October 1994).[23]

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

9.2.2. Serious Adverse Event

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

Results in death,

Is life-threatening,

Requires inpatient hospitalization or prolongation of existing hospitalization,

Results in persistent or significant disability/incapacity,

Is a congenital anomaly/birth defect, or

Is an important medical event.

Note: g≤x(ηκΔ’ (”≥yx-η≤Δxt ηκ,,≥,z (≥,,(η≤x(wxy≥,≥η≥-,,(−y(βxΔ≥πβ (ΔxyxΔβ(η−(t,,(x x,,η(≥,,(≤v≤(η≤x(subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, October 1994).[23]

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

Note:

Procedures are not AEs or SAEs, but the reason for the procedure may be an AE or SAE.

Pre-planned (prior to signing the ICF) procedures or treatments requiring hospitalizations for pre-existing conditions that do not worsen in severity are not SAEs.

9.2.3. Severity Assessment

All AEs will be graded (1 to 5; see below) according to the latest NCI-CTCAE.[24]

Grade 1 Mild AE

Grade 2 Moderate AE

Grade 3 Severe AE

Grade 4 Life-threatening consequences; urgent intervention indicated

Grade 5 Death related to AE

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

9.2.4. Causality Assessment

The Investigator should assess causal relationship between an AE and the study drugs on the basis of his/her clinical judgment and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

Related:

- The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained u (ηΣx(βπu–xvη β(v’≥„≥vt ’(βη┤ ηκ(–Δ(–ηΣxΔ(yt vη┬–Δβ((eg, disease under study, concurrent diseases, and concomitant medications).

or

- The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology.

Not Related:

- The AE does not follow a reasonable sequence from study drug administration, or vt „(ux(Δxt β–„t u” (x ×’t ≥„xw(u (ηΣx(βπu–xvη β(v’≥„≥vt ’(βη┤ ηκ(–Δ(–ηΣxΔ(yt vη┬–Δβ(lxz5(disease under study, concurrent diseases, and concomitant medications).

9.2.5. Action Taken Regarding Study Drug(s)

Dose Not Changed: No change in study drug dosage was made.

Drug Withdrawn: The study drug was permanently stopped.

Dose Reduced: The dosage of study drug was reduced.

Drug Interrupted: The study drug was temporarily stopped.

Not Applicable: Subject died, study treatment had been completed prior to reaction/event, or reaction/event occurred prior to start of treatment.

9.2.6. Other Action Taken for Event

None.

- No treatment was required.

Medication required.

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

Other.

9.2.7. Adverse Event Outcome

Recovered/Resolved

- The subject fully recovered from the AE with no residual effect observed.

Recovering/Resolving

- The AE improved but has not fully resolved.

Not Recovered/Not Resolved

- The AE itself is still present and observable.

Recovered/Resolved with Sequelae

- The residual effects of the AE are still present and observable.
- Include sequelae/residual effects.

Fatal

- Fatal should be used when death is a direct outcome of the AE.

Unknown

9.3. Adverse Events of Special Interest

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

Subjects who experience >480 ms QTcF prolongation and undergo dose interruption and/or reduction must be monitored closely with ECGs, performed twice weekly for the first week of the QTcF prolongation and then weekly thereafter until the QTcF prolongation is resolved, as described in Section 5.4.1.

Qg vR(×Δ–”–„zt ŋ≥–„(Grade 3, either serious or non-serious and whether or not causally related, must be recorded as AE or SAE in the Electronic Data Capture (EDC) system within 24 hours of awareness of the central ECG laboratory reading, with the Investigator β(t ββxββ’ x„,ŋ(–y(seriousness, causality, and a detailed narrative.[24]

9.3.2. Concurrent Elevations of Aminotransferases and Bilirubin

Concurrent elevations of aminotransferases and bilirubin, either serious or non-serious and whether or not causally related, meeting the laboratory criteria of ALT or AST = × ULN with simultaneous total bilirubin ; × ULN should always be recorded as an AE or SAE within 24 hours of awareness, with the Investigator β(t ββxββ’ x,,η(–y(βxΔ≥πβ,,xββ5(vt πβt ’≥η 5(t ,,w(t (wxη≥’xw(narrative.[24]

Subjects will be monitored as described in Section 17.1.

9.4. Safety Reporting Procedure For Investigators

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

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

SAEs (see Section 9.2.2 for definition)

d g vR(×Δ–’–,,zt η≥–,,(Grade 3, either serious or non-serious and whether or not causally related (see Section 5.4.1 for additional monitoring details)

Hepatic events meeη≥,,z(v–’ u≥,t η≥–,,(t u,,–Δ’ t ’≥η≥xβ(nM[g(–Δ(Mff g(3 × ULN with simultaneous total bilirubin ; ((h [a p5(u–η≤(βxΔ≥πβ(t ,,w(,,–,,-serious and whether or not causally related (see Section 5.4.2 for additional monitoring details)

All events (serious and non-serious) must be reported with Investigator β(t ββxββ’ x,,η(–y(η≤x(x x,,η β(βxΔ≥πβ,,xββ5(βx xΔ≥η 5(t ,,w(vt πβt ’≥η (η–(η≤x(βηπw (wΔπz7((M(wxη≥’xw(,,t Δt η≥ x(summarizing the course of the event, including its evaluation, treatment, and outcome should be provided. Specific or estimated dates of event onset, treatment, and resolution should be included when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Source documents (including medical reports) will be retained at the study site and should not be submitted to the Sponsor for SAE reporting purposes.

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

See Section 15.10.1.4 for contact information for SAE reporting. Please call the local SAE Hotline (see Study Manual) or your study monitor for any questions on SAE reporting.

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

Daiichi Sankyo and/or CRO will inform Investigators, Institutional Review Boards/Ethics Committees (IRBs/ECs), and regulatory authorities of any Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring in other study sites or other studies of the investigational drug, as appropriate per local reporting requirements. Daiichi Sankyo and/or CRO will comply with any additional local safety reporting requirements.

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9.6. Exposure In Utero During Clinical Studies

Women of childbearing potential must have negative serum pregnancy test results at times specified in the Schedule of Events (Section 17.3). If required by local regulations, additional pregnancy tests will be performed. Serum pregnancy tests will be performed at the local laboratory.

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

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

9.7. Clinical Laboratory Evaluations

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

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

1. Hematology tests

   Red blood cell count, Hgb, hematocrit, white blood cell count, differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelet count.

2. Serum chemistry tests

   Total protein, albumin, albumin/globulin ratio, total bilirubin, direct bilirubin, AST, ALT, alkaline phosphatase, gamma-glutamyl transferase, lactate dehydrogenase, creatine kinase, blood urea nitrogen, creatinine, uric acid, sodium, potassium, chloride, calcium, phosphorus, magnesium, total cholesterol, triglycerides, glucose, and C-reactive protein.

9.8. Vital Signs

Blood pressure and pulse rate will be measured after the subject has rested in a recumbent position for 5 minutes or more.

Information will be entered in the CRF on whether or not measured, date of measurement, and measurement results for the following items:

Systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, body temperature, height, and body weight. Height needs to be collected only at Screening and End-of-treatment.

9.9. Electrocardiograms

Triplicate 12-lead ECGs (3 separate ECGs) will be obtained at the times specified in the study schedule (Section 17.3). This will be performed after the subject has rested in a recumbent position for at least 5 minutes. Additional ECGs may be taken at the Investigator β(w≥βvΔxη≥−„7 The triplicate ECGs will be read in a central ECG laboratory, but the ECGs will also be reviewed by a suitably qualified physician at the study site to allow immediate decisions about subject safety. The clinical significance of any ECG change must be assessed by the Investigator in the v−„ηx η(−y(η≤x(βπu−xvη β(’ xw≥vt ’(≤βη−Δ 5(×≤ β≥vt ’(x t ’ ≥,t η≥−„,5(t „w(v−„v−’ ≥η„η(’ xw≥vt η≥−„,β7((Whether or not measurement was performed, date performed, results, and findings will be recorded in the CRF.

In Part 1 and Part 2 (excluding DDI substudy) pharmacokinetic time-matched ECG will be collected at pre-dose and 3 hours post-dose on Cycle 1/Days 1, 15, and 22, and then on Day 1 of Cycles to 2 to 6.

In Part 2 (DDI substudy) pharmacokinetic time-matched ECG will be at 0, 1, 2, 4, and 6 hours on Cycle 1/Day ; for baseline; pre-dose and 1, 2, 4, and 6 hours post-dose on Cycle 1/Days 1 and 28, Cycle 2/Days 1 and 14). Pharmacokinetic time-matched ECGs will be collected at pre-dose and 3 hours post-dose on Days 14, 15, and 22 of Cycle 1 and Day 1 of Cycles 3 to 6.

9.10. Physical Examinations

A complete physical examination (including ECOG performance status) will be performed at Screening to establish a baseline for study entry, and at additional times specified in the study schedule (Section 17.3). Whenever possible, the same individual will perform subsequent examinations to identify changes from baseline. Symptom-directed physical examinations ×xΔy−Δ’ xw(wπΔ≥„z(η≤x(ηΔxt η’ x„,η(×xΔ≥−w(≥”(ux(ut βxw(−„,(η≤x(βπu−xvη β(’ xw≥vt ’(≤βη−Δ (t „w(MQβ5(and will include weight determination and a review of body systems.

9.11. Other Examinations

Not applicable.

10. OTHER ASSESSMENTS

Not applicable.

11. STATISTICAL METHODS

11.1. General Statistical Considerations

The primary objective of this study is to assess the safety and tolerability of milademetan in combination with quizartinib and establish RDE in subjects with FLT3-ITD mutant AML.

Final data analysis for the clinical study report will occur at the end of the study when all subjects have either completed the End-of-study Follow-up or discontinued from the study or have received at least 6 months of therapy. However, the ongoing subjects deriving clinical benefit may continue to receive the treatment.

Descriptive statistics will be provided for selected demographic, safety, efficacy, PK, and available exploratory pharmacodynamic data from both dose escalation and dose expansion by dose cohort and visit as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations, minimum and maximum (as well as geometric means and geometric coefficient of variation for Cmax and AUC24h), while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented.

Assessments of change from baseline to post-treatment or the ratio of post-treatment to baseline will include only those subjects with both baseline and post-treatment measurements. The last non-missing value of a variable taken before the first dose of study drug will be used as the baseline value, unless otherwise specified. In general, missing or dropout data will not be imputed for the purpose of data analysis, unless otherwise specified.

Safety analyses will be performed based on the Safety Analysis Set. Analysis of PK parameters will be based on the PK Analysis Set. Efficacy endpoints will be analyzed based on the Full Analysis Set. Data will be summarized overall (combining subjects treated at the RDE in the dose escalation and dose expansion).

A detailed Statistical Analysis Plan (SAP) describing the methodology to be used in the final analysis will be prepared and finalized before database lock. Statistical methods described within this document may be changed based on advances in research.

11.2. Analysis Sets

The following analysis sets will be defined in this study.

Enrolled Analysis Set will include all subjects who sign the ICF.

Safety Analysis Set (and Full Analysis Set) will include all subjects who received at least 1 dose of milademetan or quizartinib.

DLT Evaluable Set will include all subjects enrolled in the dose escalation who had a DLT within Cycle 1 (28 days) on the study, or without DLT but received at least 75% scheduled dose of milademetan and quizartinib and completed the Cycle 1 evaluation.

PK Analysis Set will include all subjects in the Safety Analysis Set who have sufficient plasma concentration data to characterize PK profile.

11.3. Study Population Data

Disposition and reasons for ending the treatment and discontinuing from the study will be summarized and listed for subjects in the Full Analysis Set.

Demographic and baseline characteristics such as age, sex, race, baseline ECOG performance status, histology, cancer stage, best response to prior chemotherapy, lines of prior regimens, and prior treatment type will be summarized for the Enrolled Analysis Set, Full Analysis Set, and Safety Analysis Set. If 2 analysis sets within a part of the study are identical to each other, the table will be presented only once.

Study drug exposure, treatment duration, and compliance with study therapy will be summarized using descriptive statistics for the Safety Analysis Set.

11.4. Efficacy Analyses

The secondary endpoints of efficacy will include the rates of CR, CRi, CRc, MLFS, PR, SD, ORR, and DOR, according to Investigator s assessment (Section 2.4.3, Section 17.4, and Section 17.5). Transplantation rate and transfusion independence will be based on data reported by study sites. Stable disease rate will be summarized when SD has persisted for at least 3 months. Additionally, CRh rate will be evaluated separately from the other response criteria. The efficacy endpoints will be listed and summarized using descriptive statistics based on the FAS by dose cohort for dose escalation and dose expansion.

For response rates (CRc, ORR, etc), point estimates and 2-sided 95% exact binomial confidence intervals will be provided. Time to event endpoint (DOR) will be summarized descriptively using the Kaplan Meier method.

11.5. Pharmacokinetic/Pharmacodynamic/Biomarker Analyses

11.5.1. Pharmacokinetic Analyses

Pharmacokinetic analyses will be performed on the PK Analysis Set. Plasma concentration-time data for milademetan, quizartinib, and AC886 will be listed, plotted, and summarized using descriptive statistics by dose cohort at each timepoint. Pharmacokinetic parameters (Cmax, AUC24h, time to reach maximum plasma concentration [Tmax], trough plasma concentration [Ctrough]) will be calculated for each subject as possible. The PK parameters will be listed and summarized using descriptive statistics by dose cohort and study day.

In the DDI substudy of 12 subjects in the dose expansion part, Cmax and AUC24h for milademetan, quizartinib, and AC886 will be calculated and summarized on Cycle 1/Day 1 (milademetan only), Cycle 1/Day 28 (quizartinib, and AC886 only), Cycle 2/Day 1, and Cycle 2/Day 14.

Effects of quizartinib after repeated doses on single dose milademetan PK (Cmax and AUC24h) will be assessed by analysis of variance (ANOVA) model where reference and test treatments for milademetan PK will be Cycle 1/Day 1 and Cycle 2/Day 1, respectively. The effect of milademetan after repeated doses on steady-state quizartinib and AC886 PK (Cmax and AUC24h) will also be evaluated using an ANOVA model where the reference and test treatments for quizartinib and AC886 PK will be Cycle 1/Day 28 and Cycle 2/Day 14, respectively. The PK parameters will be transformed prior to analysis using a natural logarithm-transformation.

The 90% confidence intervals for the ratios of the geometric means for the PK parameters (Cmax and AUC24h) will be calculated.

A population PK model may be developed to assess the PK of milademetan and quizartinib/AC886. The relationship between PK and clinical response defined as the key primary and secondary endpoints may be assessed. The population PK and efficacy response analyses may be reported separately from the clinical study report.

11.5.2. Pharmacodynamic/Biomarker/Pharmacogenomic Analyses

AML blasts from bone marrow and peripheral blood for expression of p53 downstream genes (eg, MDM2, MIC-1, PUMA, NOXA, Bax, CXCL12), and downstream genes of FLT3 constitutive signaling (eg, Mcl-1, Bcl2 c-MYC) will be presented descriptively by dose cohort in the Safety Analysis Set. In addition, changes in LSCs and circulating proteins such as MIC-1 may be presented by dose cohort.

11.6. Safety Analyses

Safety analysis will be performed using the Safety Analysis Set and subjects will be analyzed according to their actual treatment received. Safety endpoints will include TEAEs, SAEs, DLTs, physical examination findings (including ECOG performance status), vital sign measurements, standard clinical laboratory parameters (serum chemistry and hematology), and ECG parameters (including QTcF). Adverse events and laboratory test results will be graded according to the NCI-CTCAE version 5.0.

Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics. In the dose escalation part, the number of DLTs identified in the DLT Evaluable Set will be listed by dose cohort.

11.6.1. Adverse Event Analyses

A TEAE is defined as an AE that emerges during the treatment period (from first dose date until 30 [± 5] days after the last dosing date), having been absent at pre-treatment; or re-emerges during treatment, having been present at baseline but stopped prior to treatment; or worsens in severity after starting treatment relative to the pre-treatment state, when the AE is continuous.

The number and percentage of subjects reporting TEAEs will be tabulated by the worst NCI-CTCAE grade, system organ class (SOC), and preferred term. Similarly, the number and percentage of subjects reporting treatment-emergent SAEs will be tabulated, as well as TEAEs/SAEs considered related to milademetan and/or quizartinib.

A by-subject AE (including TEAE) data listing will be provided including, but not limited to, verbatim term, preferred term, SOC, NCI-CTCAE grade, and relationship to study drug.

Deaths, other SAEs, and other significant AEs, including those leading to permanent discontinuation from milademetan and/or quizartinib, will be listed.

11.6.2. Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for the clinical laboratory results and changes from baseline by scheduled time of evaluation, including the End-of-treatment visit, maximum post-treatment value, and minimum post-treatment value.

Abnormal laboratory results will be graded according to NCI-CTCAE version 5.0, if applicable, and the grade will be presented in a by-subject data listing. A shift table, presenting by treatment cohort the 2-way frequency tabulation for baseline and the worst post-treatment value according to the CTCAE grade, will be provided for clinical laboratory tests. Abnormal clinical laboratory test results deemed of clinical significance or of Grade 3 or 4 will be listed.

11.6.3. Vital Sign Analyses

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

11.6.4. Electrocardiogram Analyses

Electrocardiogram parameters (PR, RR, QRS, QT, and QTcF) will be summarized using descriptive statistics for actual values and for changes from baseline by scheduled time of evaluation, including the End-of-treatment visit and the maximum post-treatment value. The v−ΔΔxvηκw(d g (≥,ηκΔ t ’β(πβ≥,z(RΔ≥wxΔ≥v≥t β(y−Δ’ π’ŧ (≥”ζux(vt ’ŧvπ’ŧ ηκw(t β(y−”’– βH(QTcF = QT/(RR)$^{1/3}$.

The incidence of notable ECG changes in maximum absolute QT and QTcF intervals (>450 ms, >480 ms, and >500 ms) over all post-treatment evaluations, as well as in QT and QTcF maximum changes from baseline (>30 ms and >60 ms) over all post-treatment evaluations will be summarized. A listing of ECG data will be provided.

11.6.5. Other Safety Analyses

Physical examination findings (including ECOG performance status) will be listed for the Safety Analysis Set. The ECOG performance status will be summarized for the Safety Analysis Set. A shift table, presenting the 2-way frequency tabulation for baseline and post-baseline visits will be provided for ECOG performance status.

11.7. Other Endpoint Analyses

Not applicable.

11.8. Interim Analyses

No formal interim analysis is planned, except for the assessment of the MTD/RDE after each escalation cohort in the dose escalation part.

11.9. Data Monitoring Committee

Not applicable.

11.10. Sample Size Determination

The dose escalation part of this study will be guided by a BLRM for dual agent combination and governed by the EWOC principle. Because of the adaptive nature of the dose escalation part of the trial, the exact sample size is unknown. Based on prior assumptions and simulations, the sample size is expected to have a median of 21 subjects. Approximately 24 to 36 DLT-evaluable subjects are needed to determine the MTDs and RDE.

In the dose expansion part, there are 2 planned cohorts. Simon 2-stage optimal design will be used to implement a futility stop. Hypotheses regarding the rates (CR/CRi plus MLFS) for the combination to be tested are H_0: p <15% and H_1: p >30% with 1-sided alpha = 0.10 and 80% power. At stage 1, a futility analysis will be conducted when Investigator-assessed best response from the first 2 cycles of study treatment are available in 19 evaluable subjects. If CR/CRi plus MLFS has been achieved as the best response prior to Cycle 3/Day 1 in less than 4 out of 19 evaluable subjects, enrollment will be stopped. Otherwise, the enrollment for stage 2 will be completed with an addition of approximately 20 subjects (for a total of 39 subjects evaluable for best response in both stage 1 and stage 2). This futility analysis will be conducted for cohort 1 (R/R AML) and cohort 2 (newly diagnosed AML), separately. The sample size for the DDI substudy was selected based on practical considerations.

11.11. Statistical Analysis Process

The clinical study will be analyzed by the Sponsor or its agent/CRO.

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

To preserve the integrity of the statistical analysis and clinical study conclusions, the SAP will be finalized prior to database lock.

All statistical analyses will be performed using SAS® Version 9.3 or higher (SAS Institute, Cary, NC 27513).

11.12. Specification of Bayesian Logistic Regression Model With Escalation With Overdose Control

11.12.1. Bayesian Logistic Regression Model With Escalation With Overdose Control

The dose-toxicity relationship using the EWOC principle for single agent will be described by a 2-parameter BLRM.[14]

”–z≥ηl lw22(I (”–z1 2(4((”–z lw8w325(>95(>0

where

$$\text{logit}(\pi(d)) = \ln \frac{\pi(d)}{1-\pi(d)}$$

t „w(lw2(≥β(η≤x(×Δ–ut u≥”≥η (–y(t (P [g (–Δ(η≤x(P [g (Δt ηκ(t η(w–βx(w7 Doses are rescaled as d/d* with the reference dose (d* = 160 mg for milademetan and 60 mg for quizartinib). As a consequence, ”–z1 2(≥β(xαπt ”(η–(”–z≥ηl lw322(t η(w–βx(w37(Note that for a dose equal to zero, the probability of toxicity is zero.

For dual agents, the dual-combination model is defined by 2 logistic single agent models with an interaction between 2 agents and the model contains 5 parameters.[14] In the 5-parameter model, 2 ×t Δt ’ xηκΔβ(l”–z1 1252”–z1 1)) characterize 2-parameter BLRM for milademetan, 2 parameters

l”–z1 ₂25(”–z1 ₂)) are used for quizartinib BLRM, and the fifth parameter (log-odds-’ π’ŋ≥×’≥xΔ5(2(will fit the interaction between milademetan and quizartinib.

11.12.2. Prior Specification for Bayesian Logistic Regression Model Parameters

The Bayesian approach requires the specification of a prior distribution for the BLRM parameters. A bivariatx(„–Δ t’(×Δ≥–Δy–Δ(ŋ≤x(’ –wx’(×t Δ‘ xŋκΔβ(l”–z1 25”–z1 22(≥β(x’≥v≥ŋκw(ut βxw(on prior assumptions about the medians from existing clinical data and confidence intervals for the probabilities of a DLT at each dose.

Prior specification of BLRM parameters (log(₁25(”–z1 ₁)) for miladem etan will based on existing DLT data (qd 21/28 dosing schedule) from Study DS3032-A-U102. The median prior probabilities of DLT are computed to be approximately 1% and 19% for 90 mg (starting dose) and 160 mg (reference dose), respectively. Prior credible intervals (obtained from informative beta distributions using Study DS3032-A-U102 data) will be used for prior tuning.

For pΔ≥–Δ(β×xv≥y≥vt ŋ≥–„(–y(l”–z1 ₂25(”–z1 ₂)) for quizartinib, the median prior probabilities of DLT from existing quizartinib studies are estimated to be approximately 5% and 17% for 30 mg (starting dose) and 60 mg (reference dose), respectively. Wide prior credible intervals (obtained from minimally informative beta distributions) will be used for prior tuning.

For the remaining doses, the medians of probability of DLT are assumed to be linear in log-dose on the logit-scale. There was no *a priori* evidence for interaction between the 2 compounds, but considerable uncertainty remained. The uncertainty was incorporated as follows: the upper 97.5% quantile for the odds-multiplier was set to 9 at the combination dose ($d1^*$, $d2^*$) = (160 mg, 60 mg). From these specifications, the prior for η allows for synergistic and antagonistic interaction between 2 agents.

Based on the above assumptions, the optimal parameters of the dual-combination BLRM model can be estimated using EAST software (version 6.4, Cytel Inc.) with ESCALATE module as follows:

Parameters	Means	Standard deviations	Correlation
”–z1 ₁25(”–z1 ₁)	17>A95(97EA>	97C>95(97=D.	9
”–z1 ₂25(”–z1 ₂)	1.586, 0.673	0.964, 0.947	0
	0	1.121	

The parameters may be adjusted based on data from ongoing studies with the same study medication.

11.12.3. Escalation With Overdose Control Principle

Dose recommendation for the next cohort will be based on summaries of the posterior probability of the DLT rate for possible combination doses of miladem etan (90 mg, 120 mg, 160 mg qd 14/28) and quizartinib (30 mg, 40 mg, and 60 mg qd 28/28). After each cohort of subjects completes the DLT evaluation during Cycle 1, the posterior distributions of the DLT rate are derived for all provisional dose levels based on the BLRM using the DLT outcome data from all assessed doses and a prespecified prior distribution for the model parameters. The

posterior probability of the DLT rate in the following 3 intervals at each dose level will be calculated and used for dose recommendation for the next cohort according to the EWOC principle:

[0%, 16%) as the underdosing DLT rate interval

[16%, 33%) as the target DLT rate interval

[33%, 100%] as the overdosing DLT rate interval

It is therefore conceivable that the posterior probability of DLT rate for dose recommendation may be generated using alternative provisional doses as long as the predicted exposure increments are between 30% and 100%.

The EWOC principle requires that the recommended dose for the next cohort of subjects is the one with the highest posterior probability of the DLT rate in the target DLT rate interval of [16%, 33%) among all doses fulfilling the overdose control constraint: there is <25% of probability for the overdosing (<25% of probability of DLT rate falling in overdosing DLT rate interval [33%, 100%]). In addition, the mean of the posterior distribution of DLT target rate at

12. DATA INTEGRITY AND QUALITY ASSURANCE

12.1. Monitoring and Inspections

The Sponsor or CRO monitor and Regulatory Authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (eg, CRFs, source data, and other pertinent documents).

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

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

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

Ų„(t vv−Δwt „vx(≥ɲ(ŲOT (S Oc (t „w(ɳ≤x(f ×−„β−Δβ(t πw≥ɲ(×’ŧ „β5(ɳ≤β(βɲπw (site may be selected for audit by representatives from the Sponsor. Audit of study site facilities (eg, pharmacy, drug storage areas, laboratories) and review of study-related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The Investigator should respond to audit findings. In the event that a Regulatory Authority informs the Investigator that it intends to conduct an inspection, the Sponsor shall be notified immediately.

12.2. Data Collection

Daiichi Sankyo or a designee will supply electronic CRFs (eCRFs). An eCRF must be completed for each subject who signs an ICF and undergoes any screening procedure. If a subject is not treated, the reason must be recorded on the eCRF. All data collected during the study will be recorded in this individual, subject-specific eCRF. Instructions will be provided for the completion of the eCRF and any corrections made will be automatically documented via the EDC software s audit trail.

Completion of the eCRF should be kept current to enable the monitor to review the subject s status throughout the course of the study. All information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood. The eCRF will be completed, reviewed and signed off or e-signed by the Investigator. The Investigator will sign and date the indicated places on the eCRF via the EDC system s electronic signature. These signatures will indicate that the Investigator inspected or reviewed the data on the eCRF, the data queries, and the site notifications, and agrees with the content.

12.3. Data Management

This is an open-label study.

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

To ensure the quality of clinical data across all subjects and study sites, a Clinical Data Management review will be performed on subject data according to specifications given to the CRO. Data will be vetted both electronically and manually for CRFs and the data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the EDC application. During this review, subject data will be checked for consistency, completeness and any apparent discrepancies. To resolve any questions arising from the Clinical Data Management review process, eCRFs queries will be raised and resolved within the EDC application.

Data received from external sources such as central labs will be reconciled to the clinical database.

Serious AEs in the clinical database will be reconciled with the safety database.

All AEs will be coded using MedDRA. All prior cancer therapy and prior or concomitant medications entered into the database will be coded by using the World Health Organization Drug Dictionary.

12.4. Study Documentation and Storage

The Investigator will maintain a Signature List of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Signature List.

Investigators will maintain a confidential Screening Log of all potential study candidates that includes limited information of the subjects, date and outcome of screening process.

Investigators will be expected to maintain an Enrollment Log of all subjects enrolled in the study indicating their assigned study number.

Investigators will maintain a confidential subject identification code list. This confidential list of names of all subjects allocated to study numbers on enrolling in the study allows the Investigator to reveal the identity of any subject when necessary.

f −πΔvx(w−vπ’ x,,ηβ(t Δx(−Δ≅z≥,t ’(w−vπ’ x,,ηβ5(wt ηt 5(t ,,w(Δxv−Δwβ(yΔ−’ (≤>v≤(η≤x(βπu−xvη β(Oe R(wt ηt (are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence.

Records of subjects, source documents, monitoring visit logs, data correction forms, CRFs, inventory of study drug, regulatory documents (eg, protocol and amendments, IRB/EC correspondence and approvals, approved and signed ICFβ5(U, xβη≥zt η−Δβ(MzΔxx’ x,,η5(clinical supplies receipts, distribution and return records), and other Sponsor correspondence pertaining to the study must be kept in appropriate study files at the study site (Trial Master File). Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or study site

policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

12.5. Record Keeping

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

Subject files containing completed CRFs, ICFs, and supporting copies of source documentation (if kept).

Study files containing the protocol with all amendments, Investigator β(NΔ–v≤πΔx5(copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the EC/IRB and the Sponsor.

Records related to the study drugs including acknowledgment of receipt at study site, accountability records and final reconciliation and applicable correspondence.

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

All study-related essential documentation will be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have lapsed since the formal discontinuation of clinical development of the investigational drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

Subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

No study document should be destroyed without prior written agreement between Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify Sponsor in writing of the new responsible person and/or the new location.

13. FINANCING AND INSURANCE

13.1. Finances

Prior to starting the study, the Principal Investigator and/or institution will sign a clinical study agreement with Daiichi Sankyo. This agreement will include the financial information agreed upon by the parties.

13.2. Reimbursement, Indemnity, and Insurance

The Sponsor provides insurance for study subjects to make available compensation in case of study-related injury.

Reimbursement, indemnity, and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

14. PUBLICATION POLICY

CCI

[redacted]

15. ETHICS AND STUDY ADMINISTRATIVE INFORMATION

15.1. Compliance Statement, Ethics, and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s) including the following:

European Commission Directive (2001/20/EC Apr 2001) and/or;

European Commission Directive (2005/28/EC Apr 2005) and/or;

US Food and Drug Administration (FDA) GCP Regulations: Code of Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56 and 312 as appropriate and/or;

Japanese Ministry of Health, Labor and Welfare Ordinance No. 28 of 27 March, 1997 and/or;

The Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics No. 1 of 25 November, 2014;

Other applicable local regulations.

15.2. Subject Confidentiality

The Investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

The Investigator ’ πβη(x„βπΔx(η≤t η(η≤x(βπu–xvη β(t „–„ ’ ≥η (≥β(’ t≥„η≥„xw7((b „(η≤x(Oe Rβ(–Δ(–ηher documents submitted to the Sponsor or the CRO, subjects should be identified by a unique subject identifier as designated by the Sponsor. Documents that are not for submission to the Sponsor or the CRO (eg, signed ICF) should be kept in strict confidence by the Investigator.

In compliance with ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/EC w≥Δxvη(t vvxββ(η–(Δx ≥x (η≤x(βπu–xvη β(–Δ≥z≥„t ’(’ xw≥vt ’(Δxv–Δwβ(y–Δ(xΔ≥y≥vt η≥–„(–y(βηπwy-related procedures and data. The Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above named representatives without violating the confidentiality of the subject.

15.3. Informed Consent

Before a subjevη β(×t Δ≥v≥×t η≥–„(≥„(η≤x(βπw 5≥η(≥β(η≤x(Investigator β(Δxβ×–„β≥u≥”≥η (η–(–uη≥„(yΔxx” (given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or any study drugs are administered. Subjects should be given the opportunity to ask questions and receive satisfactory answers to their inquiries, and should have adequate time to decide whether or not to participate in the study. The written ICF should be prepared in the local language(s) of the potential subject population.

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the EC or IRB prior to being provided to potential subjects.

g≤x(βπu–xvηβ(Δ≥ηηκ,,(≥,,y–Δ' xw(v–,,βx,,ηζβ≤–π'ẁ(ux(w–vπ' x,,ηκw(≥,,(η≤x(βπu–xvηβ(' xw≥vt'ΐ(Δκv–Δwβ7(The ICF should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily the Investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject. The date and time (if applicable) that informed consent was given should be recorded on the CRF.

Suggested model text for the ICF for the study and any applicable subparts (genomic, PK, etc) tΔκ(×Δ– ≥wxw(≥,,(η≤x(f×–,,β–Δβ(UΘR(ηκ' ×'ὶ ηκ(y–Δ(η≤x(U, xβη≥zt η–Δ(η–(×Δκ×t Δκ(η≤x(w–vπ' x,,ηβ(η–(ux(used at his or her study site. Updates to applicable forms will be communicated via letter from the Sponsor.

For study sites in the US, an additional consent is required for the Health Insurance Portability and Accountability Act. Also, a separate special consent will be required for Pharmacogenomic testing for this protocol.

15.4. Regulatory Compliance

The study protocol, subject information and consent form, the Investigator βBrochure, any written instructions to be given to the subject, available safety information, subject recruitment procedures (eg, advertisements), information about payments and compensation available to the subjects, t,,w(w–vπ' x,,η η≥–,,(x ≥wx,,v≥,,z(η≤x(U, xβη≥zt η–Δβ(απt'≥y≥vt η≥–,,β(β≤–π'ẁ(ux(βπu' ≥ηκw(η–(the EC or IRB for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the SAP.

The Sponsor will appoint a Coordinating Investigator. Among other possible duties, the Coordinating Investigator will be responsible for reviewing and approving the final clinical study report and testifying to the accuracy of the description of the study conduct. Because the Coordinating Investigator should have personal knowledge of the conduct of the study, he or she will normally be chosen from among those Investigators who have enrolled and treated at least 1 subject. However, where an Investigator has special knowledge of the field or of the trial, the Coordinating Investigator can be chosen prior to enrolment of the first subject. In all cases, the Coordinating Investigator must be chosen prior to locking the database.

The Investigator and/or Sponsor must submit and, where necessary, obtain approval from the EC or IRB for all subsequent protocol amendments and changes to the ICF. The Investigator should notify the EC or IRB of deviations from the protocol or SAEs occurring at the study site and other AE reports received from the Sponsor/CRO, in accordance with local procedures.

Mβ(Δκαπ≥Δκw(u ('–vt'ΐ(Δκzπ'ὶ η≥–,,β5(η≤x(f×–,,β–Δβ('–vt'ΐ(e xzπ'ὶ η–Δ (Myyt≥Δβ(zΔ–π×(–Δ(Δκ×Δκβx,,ηη≥ x(to whom this responsibility has been delegated will ensure all legal aspects are covered, and approval from the appropriate regulatory bodies obtained, prior to study initiation. If changes to

the initial protocol and other relevant study documents are made, this representative will also ensure that any revised documents required for submission are submitted to regulatory authorities and implementation of these changes happen only after approval by the relevant regulatory bodies, as required.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Regulatory Authority(ies) in any area of the world, or if the Investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational drug, the Sponsor should be informed immediately.

In addition, the Investigator will inform the Sponsor immediately of any urgent safety measures taken by the Investigator to protect the study subjects against any immediate hazard, and of any suspected/actual serious GCP non-compliance that the Investigator becomes aware of.

15.5. Protocol Deviations

The Investigator should conduct the study in compliance with the protocol agreed to by Sponsor and, if required, by the Regulatory Authority(ies), and which was given approval/favorable opinion by the IRBs/ECs.

A deviation to any protocol procedure or waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the subject. Sponsor must be notified of all intended or unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

The Investigator, or person designated by the Investigator, should document and explain any deviation from the approved protocol.

If a subject was ineligible or received the incorrect dose or study treatment, and had at least 1 administration of study drug, data should be collected for safety purposes.

If applicable, the Investigator should notify the IRB/EC of deviations from the protocol in accordance with local procedures.

15.6. Supply of New Information Affecting the Conduct of the Study

When new information becomes available that may adversely affect the safety of subjects or the conduct of the study, the Sponsor will inform all Investigators involved in the clinical study, ECs/IRBs, and regulatory authorities of such information, and when needed, will amend the protocol and/or subject information.

The Investigator should immediately inform the subject whenever new information becomes t t≥'t u'x(ηξt η(' t (ux(Δx'x t„,η(η–(ηξx(βπu–xvη β(v–„,βx„,η(–Δ(' t (≥„,y'πx„,vx(ηξx(βπu–xvη β(≥''≥„,z„,xββ(to continue participation in the study. The communication should be documented on medical records, for example, and it should be confirmed whether the subject is willing to remain in the study.

If the subject information is revised, it must be re-approved by the IEC/IRB. The Investigator should obtain written informed consent to continue participation with the revised written information even if subjects were already informed of the relevant information. The Investigator or other responsible personnel who provided explanations and the subject should sign and date the revised ICF.

15.7. Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the Investigator by Daiichi Sankyo or the CRO. Also, the Sponsor will ensure the timely submission of amendments to regulatory authorities.

A global protocol amendment will affect study conduct at all study sites in all regions of the world. Such amendments will be incorporated into a revised protocol document. Changes made by such amendments will be documented in a Summary of Changes document. These protocol amendments will undergo the same review and approval process as the original protocol.

A local protocol amendment will affect study conduct at a particular study site(s) and/or in a particular region/country. Sponsor approval of local amendments will be clearly documented.

A protocol amendment may be implemented after it has been approved by the IRB/EC and by regulatory authorities (*please note that this is not applicable in the EU; non-substantial protocol amendments may be implemented without IRB/EC and regulatory approval*) where appropriate, unless immediate implementation of the change is necessary for subject safety.

15.8. Study Termination

The Sponsor reserves the right to close a study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed. Reasons for study termination may include, but are not limited to:

AEs unknown to date (ie, not previously reported in any similar investigational drug study with respect to their nature, severity, and/or duration).

Increased frequency and/or severity and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at Check-in as baseline signs and symptoms).

Medical or ethical reasons affecting the continued performance of the study.

Difficulties in the recruitment of subjects.

Cancellation of drug development.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Reasons for the early closure of a study site by the Sponsor or Investigator may include, but are not limited to:

Failure of the Investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or GCP guidelines.

Inadequate recruitment of subjects by the Investigator.

15.9. Data and Safety Monitoring Board

Not applicable.

15.10. Address List

A list of key study personnel (including personnel at the Sponsor, CRO, laboratories, and other vendors) and their contact information (address, telephone, fax, email) will be kept on file and regularly updated as necessary.

15.10.1. Sponsor

Daiichi Sankyo, Inc.
211 Mount Airy Rd.
Basking Ridge, NJ 07920, US

15.10.1.1. Sponsor's Responsible Medical Officer

PPD

Senior Director, Global Oncology Research and Development

PPD

15.10.1.2. Sponsor's Clinical Scientist

PPD

Senior Director, Global Oncology Research and Development

PPD

15.10.1.3. Sponsor's Clinical Study Manager /Delivery Lead

PPD

Sr. Clinical Study Manager, Clinical Development Operations

PPD

15.10.1.4. Sponsor's Safety Contacts

PPD

Senior Director, Clinical Safety and Pharmacovigilance

PPD

15.10.1.5. Sponsor's Biostatistician

PPD

Director, Biostatistics and Data Management

PPD

15.10.2. CRO

Covance
206 Carnegie Center
Princeton, NJ 08540-6233, US
PPD

15.10.3. EDC Vendor

Chiltern International Inc
3147 S. 17th St., Suite 300
Wilmington, NC 28412, US
PPD

15.10.4. IXRS Vendor

Almac
25 Fretz Rd
Souderton, PA 18964, US
PPD

15.10.5. Central Laboratory

Covance Laboratory Services
8211 SciCor Drive
Indianapolis, IN 46214-2985, US
PPD

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17. APPENDICES

17.1. Hepatic Events and Liver Enzyme Elevation

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

ALT >8 × ULN; or

AST or ALT >5 × ULN for more than 2 weeks; or

ALT or AST >3 × ULN, but not reaching the limits in the above criteria, in combination with clinical symptoms suggestive of hepatitis; or

ALT or AST 3 × ULN with total bilirubin 2 × ULN.

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

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

Upon resumption of study drug, if liver enzyme elevations recur, treatment may be resumed at a reduced dose of milademetan and/or quizartinib following return enzymes to baseline levels.

17.1.1. Liver Safety Monitoring and Evaluations

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

Evaluation may include the following depending on the clinical situation:

Medical history and physical exam, including focus on medications and substances used: alcohol, acetaminophen, azole antifungals, change in medication dosages, new medications added, over-the-counter medication use, and recreational drug use. Check for change in diet or use of dietary supplements;

Abdominal ultrasound;

Hepatitis A, B, C, and E screening (anti-hepatitis A virus immunoglobulin M, hepatitis B surface antigen, anti-hepatitis C virus plus viral titer, and evaluation for Hepatitis E), antinuclear antibody and anti-Smith antibody, cytomegalovirus, Epstein Barr virus;

Additional evaluations as deemed appropriate by the Investigator to exclude other causes of liver enzyme and bilirubin elevations;

All laboratory results, including local laboratory reference ranges are to be recorded.

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

Sweet's syndrome can be idiopathic, malignancy-associated, or drug-induced.[25] The incidence of drug-≥„wπvxw(f xxηβ(f „wΔ–' x(lP Uf f 2(y–"'– ≥„z(R[g=(≥„≤u≥η–Δ(' –„–η≤xΔt × (≥β(approximately 10% during the treatment period in the setting of R/R AML.[26] DISS is unlikely to occur in the setting of concurrent cytoreduction with traditional chemotherapy due to suppression of terminal differentiation of FLT3-ITD myeloblasts and associated clinical manifestations.

Diagnostic criteria for DISS include abrupt onset of painful erythematous plaques or nodules, pyrexia >38°C, temporal relationship between drug ingestion and clinical presentation, temporally-related resolution of lesions after drug withdrawal or treatment with systemic corticosteroids, and histopathologic evidence of a dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis. Cardiac, pulmonary and upper airway neutrophil infiltration can present as life-threatening emergencies.[25]

The symptoms of neutrophilic dermatosis can generally be managed with systemic corticosteroid administration. Other first-line systemic treatments for Sweet's syndrome include potassium iodide and colchicine.[25] The interruption or discontinuation of quizartinib is usually not required[26,27] and discussion with the Sponsor Medical Monitor is optional. However, for advanced Grade 3 or 4 toxicities the decision to continue, interrupt or discontinue quizartinib therapy must be made by the In xβη≥z t η–Δ(ut βxw(–„(η≤x(≥„w≥ ≥wπt '(βπu–xvηβ(v–„w≥η≥–„5(η "≥„z(≥„η–(account the risks and benefits of continuing quizartinib therapy, and in consultation with the Sponsor Medical Monitor.

17.3. Schedule of Events

Table 17.1: Schedule of Events (for Part 1) – Milademetan QD 14/28 Regimen

Cycle (1 cycle = 28 days)[a]	Pre-cycle	1						2				3				4 and Beyond	Post-cycle	
Visit Description	**SCR**	**EX and 1st Dose**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EOT[b]**	**F/U[c]**
Cycle Day(s)	**−14 to −1**	**1**	**2**	**8**	**14**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**ND**	**ND**
Visit Window (days)				**± 2**			**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**		
Informed consent	X																	
SID number assigned	X																	
Demographics	X																	
Medical history	X																	
Inclusion/exclusion criteria	X																	
Pregnancy test[d]	X											X				X[e]	X	
FSH test[f]	X																	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record transfusion	X[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG	X	X		X	X			X		X		X				X	X	
Height	X																X	
Physical examination, including weight[h]	X	X		X	X			X		X		X				X	X	
Vital signs[i]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	
Safety laboratory[j]	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	
Blood for testing hepatitis B or C	X																	
Blood for testing FLT3 mutation	X																	
Triplicate ECG (12-lead)[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECHO/MUGA[l]	X																	
BM assessment	X[m]							X[m]				X[m]				X[n]		
BM for exploratory biomarker analysis[o]	X[m]							X[m]				X[m]				X[n]		
Blood for exploratory biomarker analysis[p]		X	X	X				X				X				X	X	
Blood for banking plasma[q]		X		X				X				X				X	X	

Cycle (1 cycle = 28 days)[a]	Pre-cycle	1						2				3				4 and Beyond	Post-cycle	
Visit Description	**SCR**	**EX and 1st Dose**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EOT[b]**	**F/U[c]**
Cycle Day(s)	**−14 to −1**	**1**	**2**	**8**	**14**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**ND**	**ND**
Visit Window (days)				**± 2**			**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**		
Blood for MIC-1 analysis[r]		X	X	X	X		X	X										
PGx sample[s]		X																
Quizartinib administration[t]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Milademetan administration[t]		X	X	X	X			X	X			X	X			X		
Blood sample for PK[u]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense quizartinib[v]			X	X		X	X	X	X	X	X	X	X	X	X	X		
Dispense milademetan[v]			X	X				X	X			X	X			X		
Pill diaries dispensed/reviewed[v]			X	X	X		X	X	X	X	X	X	X	X	X	X	X	
Medication compliance reviewed[v]				X	X		X	X	X	X	X	X	X	X	X	X	X	
BM re-biopsy or aspirate[w]																	X	
Follow-up survival data[x]																	X	X

AML = acute myeloid leukemia; BM = bone marrow; BMA = bone marrow aspirate; BMB = bone marrow biopsy; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS F/U = End-of-study Follow-up; EOT = End-of-treatment; EX = exam; FSH = follicle stimulating hormone; F/U = Follow-up; HCT = hematopoietic cell transplant; MUGA = multigated acquisition; ND = not determined; PD = progressive disease; PK = pharmacokinetics; SCR = Screening; SID = subject identifier.

Note: Informed consent will be obtained prior to screening procedures.

[a] Each cycle will last 28 days with quizartinib dosed once every day and milademetan qd on Days 1 to 14. Cohort safety assessment for dose-limiting toxicities will be performed at the end of Cycle 1.

[b] End-of-treatment visit will occur within 30 days after the last administration of study drug(s). If a subject begins another anticancer therapy before the end of the 30-day period, every effort will be made to complete all of the EOT assessments prior to commencing the new therapy. If there is an abnormality in need of monitoring beyond the EOT visit, subjects will be followed until resolution or confirmed stability of the abnormality, provided the subject is available for follow-up.

[c] Follow-up will occur first at 30 (± 5) days after the last dose of the study drug (this can be accomplished by a site visit or phone call if the subject cannot return to the site) and then every 3 months (± 2 weeks) until death or until Sponsor terminates study.

[d] A serum pregnancy test will be required for all female subjects of childbearing potential.

[e] Cycle 4 and beyond, a serum pregnancy test in women of childbearing potential will be required on Day 1 of every 3 cycles from Cycle 3 (ie, Cycles 6, 9, 12, etc).

[f] Obtain an FSH test in women of childbearing potential to confirm menarche.

[g] At SCR, collect transfusion history for the 56 days prior to first dose of study drugs.

[h] Physical examinations, including weight, will be performed on the indicated visit days. Physical examinations on Cycle 1/Day 1 need not be repeated if previously performed within 24 hours before the first dose.

[i] Vital sign measurements will include systolic blood pressure, diastolic blood pressure, respiratory rate, pulse rate, and body temperature. They will be collected on the indicated visits, as well as at 3 hours (± 10 minutes) post-dose on Cycle 1/Day 1.

[j] Blood samples for safety laboratories (hematology and serum chemistry) will be collected on indicated visits. Creatinine clearance will be calculated at the SCR visit. The sample for safety laboratories on Cycle 1/Day 1 need not be collected if previously collected within 72 hours prior to first dose.

[k] Electrocardiograms will be performed in triplicate at pre-dose and at 1, 2, 4, and 6 hours post-dose on Cycle 1/Days 1 and 14, and at pre-dose on other indicated visit days. On Days 15 and 22 of Cycle 1 and Day 1 of Cycles 2 to 6, ECGs will also be collected at 3 hours post-dose. The ECG should be performed within 10 minutes prior to PK sample collection. Subject should be in supine position for 5 minutes prior to each reading. Other unscheduled ECGs may be performed as clinically indicated.

[l] An ECHO/MUGA scan that was performed within 60 days before the first dose of study drugs may be used.

[m] BM samples for disease assessment and exploratory biomarkers analysis are required at SCR and pre-dose on Day 1 of Cycles 2 and 3.

[n] If subject achieves CR, CRi, or MLFS before Cycle 4/Day 1, then BMBs/BMAs will not be required on Cycle 4/Day 1. Perform BMBs/BMAs on Day 1 of Cycles 6, 9, and 12 if subject remains in CR, CRi, or MLFS. If subject does not achieve CR, CRi, or MLFS before Cycle 4/Day 1 (eg, PR on Cycle 3/Day 1), BMBs/BMAs will be required on Cycle 4/Day 1, and on Day 1 of every cycle thereafter until subject achieves CR, CRi, or MLFS. Beyond Cycle 12/Day 1, subjects who remain in CR, CRi, or MLFS on Cycle 12/Day 1 will need to undergo BMBs/BMAs on Day 1 of Cycles 18, 24, and every 6 cycles thereafter. All unscheduled BM assessments performed on non-visit days must be reported as unscheduled visits.

[o] BM samples at Screening and on Day 1 of Cycles 2, 3, 6, 9, 12, 18, 24, and every 6 cycles thereafter will be submitted for translational research. BM samples from unscheduled BMBs/BMAs should be also submitted for translational research when disease progression (relapse or progressive disease) is suspected. Additionally, submit BM samples for minimal residual disease analysis (eg, flow cytometry and/or next generation sequencing) on the day when <5% blasts in BM is observed and/or at the subsequent timepoints for BM sample collection. BM samples from other timepoints are not required to be submitted (eg, Cycle 4/Day1). Blood for exploratory biomarker analysis will be collected at the indicated timepoints in Cycle 1, and at the same timepoints as BMBs/BMAs in subsequent cycles. Refer to the Laboratory Manual for additional details and instructions.

[p] Peripheral blood collected for exploratory analysis of blasts and other pharmacodynamic circulating biomarkers at the indicated timepoints in Cycle 1, Cycle 2, and Cycle 3, and then on Day 1 of every 3-6 cycles corresponding to the timepoints for BMBs/BMAs (ie, Cycles 6, 9, 12, 18, 24, and every 6 cycles thereafter) and at EOT.

[q] Peripheral blood collected for banking plasma for future exploratory molecular analysis of biomarkers at the indicated timepoints in Cycle 1, Cycle 2, and Cycle 3, and then on Day 1 of every 3-6 cycles corresponding to the timepoints for BMBs/BMAs (ie, Cycles 6, 9, 12, 18, 24, and every 6 cycles thereafter) and at EOT.

[r] Serum will be collected from the blood obtained at the indicated timepoints for MIC-1 analysis.

[s] Informed consent specifically allowing PGx testing sample storage must be obtained before collecting sample.

[t] Quizartinib and milademetan are administered per protocol at the clinical site at the indicated visits without regard to the timing of food. Quizartinib will be dispensed for continuous qd dosing for each 28 day cycle and milademetan will be dispensed for qd dosing for 14 days of each 28-day cycle.

[u] PK samples for milademetan, quizartinib, and AC886 are collected at pre-dose and at 0.5, 1, 2, 3, 4, and 6-8 hours post-dose on Cycle 1/Days 1 and 14, and at pre-dose on all other indicated visit days. Please refer to Table 8.1 for collection schedule and other information. PK samples at pre-dose and 3 hours post-

dose will be collected on Cycle 1/Days 15 and 22, and on Day 1 of Cycles 2 to 6 with time-matched ECGs (within 10 minutes before the PK sample collection).

[v] Study drugs and pill diary may be dispensed for at-home dosage, if regionally required.

[w] A BM re-biopsy or aspirate must be performed within 30 (± 5) days of the last dose of study drug in subjects who have achieved an initial CR, CRi, MLFS, or PR to the treatment but later relapsed/developed PD while on therapy.

[x] If feasible, collect subject survival status, date and cause of death (if applicable), subsequent AML therapy, and HCT and HCT-relevant information (if performed).

Table 17.2: Schedule of Events (for Part 1) - Alternative Milademetan QD 7/28 Regimen

Cycle (1 cycle = 28 days)[a]	Pre-cycle	1						2				3				4 and Beyond	Post-cycle	
Visit Description	**SCR**	**EX and 1st Dose**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EOT[b]**	**F/U[c]**
Cycle Day(s)	**−14 to −1**	**1**	**2**	**8**	**14**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**ND**	**ND**
Visit Window (days)				**± 2**			**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**		
Informed consent	X																	
SID number assigned	X																	
Demographics	X																	
Medical history	X																	
Inclusion/exclusion criteria	X																	
Pregnancy test[d]	X											X				X[e]	X	
FSH test[f]	X																	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record transfusion	X[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG	X	X		X	X			X		X		X				X	X	
Height	X																X	
Physical examination, including weight[h]	X	X		X	X			X		X		X				X	X	
Vital signs[i]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	
Safety laboratory[j]	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	
Blood for testing hepatitis B or C	X																	
Blood for testing FLT3 mutation	X																	
Triplicate ECG (12-lead)[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECHO/MUGA[l]	X																	
BM assessment	X[m]							X[m]				X[m]				X[n]		
BM for exploratory biomarker analysis[o]	X[m]							X[m]				X[m]				X[n]		
Blood for exploratory biomarker analysis[p]		X	X	X				X				X				X	X	
Blood for banking plasma[q]		X		X				X				X				X	X	
Blood for MIC-1 analysis[r]		X	X	X	X		X	X										
PGx sample[s]		X																

Cycle (1 cycle = 28 days)[a]	Pre-cycle	1						2				3				4 and Beyond	Post-cycle	
Visit Description	**SCR**	**EX and 1st Dose**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EOT[b]**	**F/U[c]**
Cycle Day(s)	**−14 to −1**	**1**	**2**	**8**	**14**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**ND**	**ND**
Visit Window (days)				**± 2**			**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**		
Quizartinib administration[t]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Milademetan administration[t]		X	X					X				X				X		
Blood sample for PK[u]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense quizartinib[v]			X	X		X	X	X	X	X	X	X	X	X	X	X		
Dispense milademetan[v]			X					X				X				X		
Pill diaries dispensed/reviewed[v]			X	X	X		X	X	X	X	X	X	X	X	X	X	X	
Medication compliance reviewed[v]				X	X		X	X	X	X	X	X	X	X	X	X	X	
BM re-biopsy or aspirate[w]																	X	
Follow-up survival data[x]																	X	X

AML = acute myeloid leukemia; BM = bone marrow; BMA = bone marrow aspirate; BMB = bone marrow biopsy; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS F/U = End-of-study Follow-up; EOT = End-of-treatment; EX = exam; FSH = follicle stimulating hormone; F/U = Follow-up; HCT = hematopoietic cell transplant; MUGA = multigated acquisition; PD = progressive disease; PK = pharmacokinetics; SCR = Screening; SID = subject identifier; ND = not determined.

Note: Informed consent will be obtained prior to screening procedures.

[a] Each cycle will last 28 days with quizartinib dosed once every day (qd) and milademetan qd on Days 1 to 7. Cohort safety assessment for dose-limiting toxicities will be performed at the end of Cycle 1.

[b] End-of-treatment visit will occur within 30 days after the last administration of study drug(s). If a subject begins another anticancer therapy before the end of the 30-day period, every effort will be made to complete all of the EOT assessments prior to commencing the new therapy. If there is an abnormality in need of monitoring beyond the EOT visit, subjects will be followed until resolution or confirmed stability of the abnormality, provided the subject is available for follow-up.

[c] Follow-up will occur first at 30 (± 5) days after the last dose of the study drug (this can be accomplished by a site visit or phone call if the subject cannot return to the site) and then every 3 months (± 2 weeks) until death or until Sponsor terminates study.

[d] A serum pregnancy test will be required for all female subjects of childbearing potential.

[e] Cycle 4 and beyond, a serum pregnancy test in women of childbearing potential will be required on Day 1 of every 3 cycles from Cycle 3 (ie, Cycles 6, 9, 12, etc).

[f] Obtain an FSH test in women of childbearing potential to confirm menarche.

[g] At SCR, collect transfusion history for the 56 days prior to first dose of study drugs.

[h] Physical examinations, including weight, will be performed on the indicated visit days. Physical examinations on Cycle 1/Day 1 need not be repeated if previously performed within 24 hours before the first dose.

[i] Vital sign measurements will include systolic blood pressure, diastolic blood pressure, respiratory rate, pulse rate, and body temperature. They will be collected on the indicated visits, as well as at 3 hours (± 10 minutes) post-dose on Cycle 1/Day 1.

[j] Blood samples for safety laboratories (hematology and serum chemistry) will be collected on indicated visits. Creatinine clearance will be calculated at the SCR visit. The sample for safety laboratories on Cycle 1/Day 1 need not be collected if previously collected within 72 hours prior to first dose.

[k] Electrocardiograms will be performed in triplicate at pre-dose and at 1, 2, 4, and 6 hours post-dose on Cycle 1/Days 1 and 14, and at pre-dose on other indicated visit days. On Days 15 and 22 of Cycle 1 and Day 1 of Cycles 2 to 6, ECGs will also be collected at 3 hours post-dose. The ECG should be performed within 10 minutes prior to PK sample collection. Subject should be in supine position for 5 minutes prior to each reading. Other unscheduled ECGs may be performed as clinically indicated.

[l] An ECHO/MUGA scan that was performed within 60 days before the first dose of study drugs may be used.

[m] BM samples for disease assessment and exploratory biomarkers analysis are required at SCR and pre-dose on Day 1 of Cycles 2 and 3.

[n] If subject achieves CR, CRi, or MLFS before Cycle 4/Day 1, then BMBs/BMAs will not be required on Cycle 4/Day 1. Perform BMBs/BMAs on Day 1 of Cycles 6, 9, and 12 if subject remains in CR, CRi, or MLFS. If subject does not achieve CR, CRi, or MLFS before Cycle 4/Day 1 (eg, PR on Cycle 3/Day 1), BMBs/BMAs will be required on Cycle 4/Day 1, and on Day 1 of every cycle thereafter until subject achieves CR, CRi, or MLFS. Beyond Cycle 12/Day 1, subjects who remain in CR, CRi, or MLFS on Cycle 12/Day 1 will need to undergo BMBs/BMAs on Day 1 of Cycles 18, 24, and every 6 cycles thereafter. All unscheduled BM assessments performed on non-visit days must be reported as unscheduled visits.

[o] BM samples at Screening and on Day 1 of Cycles 2, 3, 6, 9, 12, 18, 24, and every 6 cycles thereafter will be submitted for translational research. BM samples from unscheduled BMBs/BMAs should be also submitted for translational research when disease progression (relapse or progressive disease) is suspected. Additionally, submit BM samples for minimal residual disease analysis (eg, flow cytometry and/or next generation sequencing) on the day when <5% blasts in BM is observed and/or at the subsequent timepoints for BM sample collection. BM samples from other timepoints are not required to be submitted (eg, Cycle 4/Day1). Blood for exploratory biomarker analysis will be collected at the indicated timepoints in Cycle 1, and at the same timepoints as BMBs/BMAs in subsequent cycles. Refer to the Laboratory Manual for additional details and instructions.

[p] Peripheral blood collected for exploratory analysis of blasts and other pharmacodynamic circulating biomarkers at the indicated timepoints in Cycle 1, Cycle 2, and Cycle 3, and then on Day 1 of every 3-6 cycles corresponding to the timepoints for BMBs/BMAs (ie, Cycles 6, 9, 12, 18, 24, and every 6 cycles thereafter) and at EOT.

[q] Peripheral blood collected for banking plasma for future exploratory molecular analysis of biomarkers at the indicated timepoints in Cycle 1, Cycle 2, and Cycle 3, and then on Day 1 of every 3-6 cycles corresponding to the timepoints for BMBs/BMAs (ie, Cycles 6, 9, 12, 18, 24, and every 6 cycles thereafter) and at EOT.

[r] Serum will be collected from the blood obtained at the indicated timepoints for MIC-1 analysis.

[s] Informed consent specifically allowing PGx testing sample storage must be obtained before collecting sample.

[t] Quizartinib and milademetan are administered per protocol at the clinical site at the indicated visits without regard to the timing of food. Quizartinib will be dispensed for continuous qd dosing for each 28-day cycle and milademetan will be dispensed for qd dosing for 7 days of each 28 day cycle.

[u] PK samples for milademetan, quizartinib, and AC886 are collected at pre-dose and at 0.5, 1, 2, 3, 4, and 6-8 hours post-dose on Cycle 1/Days 1 and 14, and at pre-dose on all other indicated visit days. Please refer to Table 8.1 for collection schedule and other information. PK samples at pre-dose and 3 hours post-dose will be collected on Cycle 1/Days 15 and 22, and on Day 1 of Cycles 2 to 6 with time-matched ECGs (within 10 minutes before the PK sample collection).

[v] Study drugs and pill diary may be dispensed for at-home dosage, if regionally required.

[w] A BM re-biopsy or aspirate must be performed within 30 (± 5) days of the last dose of study drug in subjects who have achieved an initial CR, CRi, MLFS, or PR to the treatment but later relapsed/developed PD while on therapy.

[x] If feasible, collect subject survival status, date and cause of death (if applicable), subsequent AML therapy, and HCT and HCT-relevant information (if performed).

Table 17.3: Schedule of Events (for Part 1) - Alternative Milademetan QD 3/14 × 2 Regimen

Cycle (1 cycle = 28 days)[a]	Pre-cycle	1						2				3				4 and Beyond	Post-cycle	
Visit Description	**SCR**	**EX and 1st Dose**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EOT[b]**	**F/U[c]**
Cycle Day(s)	**−14 to −1**	**1**	**2**	**8**	**14**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**ND**	**ND**
Visit Window (days)				**± 2**			**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**		
Informed consent	X																	
SID number assigned	X																	
Demographics	X																	
Medical history	X																	
Inclusion/exclusion criteria	X																	
Pregnancy test[d]	X											X				X[e]	X	
FSH test[f]	X																	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record transfusion	X[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG	X	X		X	X			X		X		X				X	X	
Height	X																X	
Physical examination, including weight[h]	X	X		X	X			X		X		X				X	X	
Vital signs[i]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	
Safety laboratory[j]	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	
Blood for testing hepatitis B or C	X																	
Blood for testing FLT3 mutation	X																	
Triplicate ECG (12-lead)[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECHO/MUGA[l]	X																	
BM assessment	X[m]							X[m]				X[m]				X[n]		
BM for exploratory biomarker analysis[o]	X[m]							X[m]				X[m]				X[n]		
Blood for exploratory biomarker analysis[p]		X	X	X				X				X				X	X	
Blood for banking plasma[q]		X		X				X				X				X	X	
Blood for MIC-1 analysis[r]		X	X	X	X		X	X										

Cycle (1 cycle = 28 days)[a]	Pre-cycle	1						2				3				4 and Beyond	Post-cycle	
Visit Description	**SCR**	**EX and 1st Dose**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EOT[b]**	**F/U[c]**
Cycle Day(s)	**−14 to −1**	**1**	**2**	**8**	**14**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**ND**	**ND**
Visit Window (days)				**± 2**			**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**		
PGx sample[s]		X																
Quizartinib administration[t]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Milademetan administration[t]		X	X			X		X		X		X		X		X		
Blood sample for PK[u]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense quizartinib[v]			X	X		X	X	X	X	X	X	X	X	X	X	X		
Dispense milademetan[v]			X			X		X		X		X		X		X		
Pill diaries dispensed/reviewed[v]			X	X	X		X	X	X	X	X	X	X	X	X	X	X	
Medication compliance reviewed[v]				X	X		X	X	X	X	X	X	X	X	X	X	X	
BM re-biopsy or aspirate[w]																	X	
Follow-up survival data[x]																	X	X

AML = acute myeloid leukemia; BM = bone marrow; BMA = bone marrow aspirate; BMB = bone marrow biopsy; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = EOS F/U = End-of-study Follow-up; EOT = End-of-treatment; EX = exam; FSH = follicle stimulating hormone; F/U = Follow-up; HCT = hematopoietic cell transplant; MUGA = multigated acquisition; ND = not determined; PD = progressive disease; PK = pharmacokinetics; SCR = Screening; SID = subject identifier.

Note: Informed consent will be obtained prior to screening procedures.

[a] Each cycle will last 28 days with quizartinib dosed once every day and milademetan qd on Days 1 to 3 and 15 to 17. Cohort safety assessment for dose limiting toxicities will be performed at the end of Cycle 1.

[b] End-of-treatment visit will occur within 30 days after the last administration of study drug(s). If a subject begins another anticancer therapy before the end of the 30-day period, every effort will be made to complete all of the EOT assessments prior to commencing the new therapy. If there is an abnormality in need of monitoring beyond the EOT visit, subjects will be followed until resolution or confirmed stability of the abnormality, provided the subject is available for follow-up.

[c] Follow-up will occur first at 30 (± 5) days after the last dose of the study drug (this can be accomplished by a site visit or phone call if the subject cannot return to the site) and then every 3 months (± 2 weeks) until death or until Sponsor terminates study.

[d] A serum pregnancy test will be required for all female subjects of childbearing potential.

[e] Cycle 4 and beyond, a serum pregnancy test in women of childbearing potential will be required on Day 1 of every 3 cycles from Cycle 3 (ie, Cycles 6, 9, 12, etc).

[f] Obtain an FSH test in women of childbearing potential to confirm menarche.

[g] At SCR, collect transfusion history for the 56 days prior to first dose of study drugs.

[h] Physical examinations, including weight, will be performed on the indicated visit days. Physical examinations on Cycle 1/Day 1 need not be repeated if previously performed within 24 hours before the first dose.

[i] Vital sign measurements will include systolic blood pressure, diastolic blood pressure, respiratory rate, pulse rate, and body temperature. They will be collected on the indicated visits, as well as at 3 hours (± 10 minutes) post-dose on Cycle 1/Day 1.

[j] Blood samples for safety laboratories (hematology and serum chemistry) will be collected on indicated visits. Creatinine clearance will be calculated at the SCR visit. The sample for safety laboratories on Cycle 1/Day 1 need not be collected if previously collected within 72 hours prior to first dose.

[k] Electrocardiograms will be performed in triplicate at pre-dose and at 1, 2, 4, and 6 hours post-dose on Cycle 1/Days 1 and 14, and at pre-dose on other indicated visit days. On Days 15 and 22 of Cycle 1 and Day 1 of Cycles 2 to 6, ECGs will also be collected at 3 hours post-dose. The ECG should be performed within 10 minutes prior to PK sample collection. Subject should be in supine position for 5 minutes prior to each reading. Other unscheduled ECGs may be performed as clinically indicated.

[l] An ECHO/MUGA scan that was performed within 60 days before the first dose of study drugs may be used.

[m] Bone marrow samples for disease assessment and exploratory biomarkers analysis are required at SCR and pre-dose on Day 1 of Cycles 2 and 3.

[n] If subject achieves CR, CRi, or MLFS before Cycle 4/Day 1, then BMBs/BMAs will not be required on Cycle 4/Day 1. Perform BMBs/BMAs on Day 1 of Cycles 6, 9, and 12 if subject remains in CR, CRi, or MLFS. If subject does not achieve CR, CRi, or MLFS before Cycle 4/Day 1 (eg, PR on Cycle 3/Day 1), BMBs/BMAs will be required on Cycle 4/Day 1, and on Day 1 of every cycle thereafter until subject achieves CR, CRi, or MLFS. Beyond Cycle 12/Day 1, subjects who remain in CR, CRi, or MLFS on Cycle 12/Day 1 will need to undergo BMBs/BMAs on Day 1 of Cycles 18, 24, and every 6 cycles thereafter. All unscheduled BM assessments performed on non-visit days must be reported as unscheduled visits.

[o] BM samples at Screening and on Day 1 of Cycles 2, 3, 6, 9, 12, 18, 24, and every 6 cycles thereafter will be submitted for translational research. BM samples from unscheduled BMBs/BMAs should be also submitted for translational research when disease progression (relapse or progressive disease) is suspected. Additionally, submit BM samples for minimal residual disease analysis (eg, flow cytometry and/or next generation sequencing) on the day when <5% blasts in BM is observed and/or at the subsequent timepoints for BM sample collection. BM samples from other timepoints are not required to be submitted (eg, Cycle 4/Day1). Blood for exploratory biomarker analysis will be collected at the indicated timepoints in Cycle 1, and at the same timepoints as BMBs/BMAs in subsequent cycles. Refer to the Laboratory Manual for additional details and instructions.

[p] Peripheral blood collected for exploratory analysis of blasts and other pharmacodynamic circulating biomarkers at the indicated timepoints in Cycle 1, Cycle 2, and Cycle 3, and then on Day 1 of every 3-6 cycles corresponding to the timepoints for BMBs/BMAs (ie, Cycles 6, 9, 12, 18, 24, and every 6 cycles thereafter) and at EOT.

[q] Peripheral blood collected for banking plasma for future exploratory molecular analysis of biomarkers at the indicated timepoints in Cycle 1, Cycle 2, and Cycle 3, and then on Day 1 of every 3-6 cycles corresponding to the timepoints for BMBs/BMAs (ie, Cycles 6, 9, 12, 18, 24, and every 6 cycles thereafter) and at EOT.

[r] Serum will be collected from the blood obtained at the indicated timepoints for MIC-1 analysis.

[s] Informed consent specifically allowing PGx testing sample storage must be obtained before collecting sample.

[t] Quizartinib and milademetan are administered per protocol at the clinical site at the indicated visits without regard to the timing of food. Quizartinib will be dispensed for continuous qd dosing for each 28 day cycle and milademetan will be dispensed for qd dosing at home for Days 2 to 3 and Days 16 to 17 of each 28 day cycle.

[u] PK samples for milademetan, quizartinib, and AC886 are collected at pre-dose and at 0.5, 1, 2, 3, 4, and 6-8 hours post-dose on Cycle 1/Days 1 and 14, and at pre-dose on all other indicated visit days. Please refer to Table 8.1 for collection schedule and other information. PK samples at pre-dose and 3 hours post-

dose will be collected on Cycle 1/Days 15 and 22, and on Day 1 of Cycles 2 to 6 with time-matched ECGs (within 10 minutes before the PK sample collection).

[v] Study drugs and pill diary may be dispensed for at-home dosage, if regionally required.

[w] A BM re-biopsy or aspirate may be performed within 30 (± 5) days of the last dose of study drug in subjects who have achieved an initial CR, CRi, MLFS, or PR to the treatment but later relapsed/developed PD while on therapy.

[x] If feasible, collect subject survival status, date and cause of death (if applicable), subsequent AML therapy, and HCT and HCT-relevant information (if performed).

Table 17.4: Schedule of Events (for Part 2, Except Subjects in DDI Substudy) – Milademetan QD 14/28 Regimen[§]

Cycle (1 cycle = 28 days)[a]	Pre-cycle	1						2				3				4 and Beyond	Post-cycle TBD	
Visit Description	**SCR**	**EX and 1st Dose**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EOT[b]**	**F/U[c]**
Cycle Day(s)	**−14 to −1**	**1**	**2**	**8**	**14**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**ND**	**ND**
Visit Window (days)				**± 2**			**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**		
Informed consent	X																	
SID number assigned	X																	
Demographics	X																	
Medical history	X																	
Inclusion/exclusion criteria	X																	
Pregnancy test[d]	X											X				X[e]	X	
FSH test[f]	X																	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record transfusion	X[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG	X	X		X	X			X				X				X	X	
Height	X																X	
Physical examination, including weight[h]	X	X		X	X			X				X				X	X	
Vital signs[i]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	
Safety laboratory[j]	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	
Blood for testing hepatitis B or C	X																	
Blood for testing FLT3 mutation	X																	
Triplicate ECG (12-lead)[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECHO/MUGA[l]	X																	
BM assessment	X[m]							X[m]				X[m]				X[n]		
BM for exploratory biomarker analysis[o]	X[m]							X[m]				X[m]				X[n]		

Cycle (1 cycle = 28 days)[a]	Pre-cycle	1						2				3				4 and Beyond	Post-cycle TBD	
Visit Description	**SCR**	**EX and 1st Dose**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EOT[b]**	**F/U[c]**
Cycle Day(s)	**−14 to −1**	**1**	**2**	**8**	**14**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**ND**	**ND**
Visit Window (days)				**± 2**			**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**		
Blood for exploratory biomarker analysis[p]		X	X	X				X				X				X	X	
Blood for banking plasma[q]		X		X				X				X				X	X	
Blood for MIC-1 analysis[r]		X	X	X	X		X	X										
PGx sample[s]		X																
Quizartinib administration[t]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Milademetan administration[t]		X	X	X	X			X	X			X	X			X		
Blood sample for PK[u]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense quizartinib[v]			X	X		X	X	X	X	X	X	X	X	X	X	X		
Dispense milademetan[v]			X	X				X	X			X	X			X		
Pill diaries dispensed/reviewed[v]			X	X	X		X	X	X	X	X	X	X	X	X	X	X	
Medication compliance reviewed[v]				X	X		X	X	X	X	X	X	X	X	X	X	X	
BM re-biopsy or aspirate[w]																	X	
Follow-up survival data[x]																	X	X

AML = acute myeloid leukemia; BM = bone marrow; BMA = bone marrow aspirate; BMB = bone marrow biopsy; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS F/U = End-of-study Follow-up; EOT = End-of-treatment; EX = exam; FSH = follicle stimulating hormone; F/U= Follow-up; HCT = hematopoietic cell transplant; MUGA = multigated acquisition; ND = not determined; PD = progressive disease; PK = pharmacokinetics; SCR = Screening; SID = subject identifier; TBD = to be determined.

Note: Informed consent will be obtained prior to screening procedures.

§ If RDE is determined in a different dosing schedule of milademetan than qd 14/28, the protocol will be amended to accommodate the schedule of events for Part 2 according to the RDE dosing schedule.

[a] Each cycle will last 28 days with quizartinib dosed once every day and milademetan dosed qd on Days 1 to 14. Cohort safety assessment for dose limiting toxicities will be performed at the end of Cycle 1.

[b] End-of-treatment visit will occur within 30 days after the last administration of study drug(s). If a subject begins another anticancer therapy before the end of the 30 day period, every effort will be made to complete all of the EOT assessments prior to commencing the new therapy. If there is an abnormality in need of monitoring beyond the EOT visit, subjects will be followed until resolution or confirmed stability of the abnormality, provided the subject is available for follow-up.

[c] Follow-up will occur first at 30 (± 5) days after the last dose of the study drug (this can be accomplished by a site visit or phone call if the subject cannot return to the site) and then every 3 months (± 2 weeks) until death or until Sponsor terminates study.

[d] A serum pregnancy test will be required for all female subjects of childbearing potential.

[e] Cycle 4 and beyond, a serum pregnancy test in women of childbearing potential will be required on Day 1 of every 3 cycles from Cycle 3 (ie, Cycles 6, 9, 12, etc).

[f] Obtain an FSH test in women of childbearing potential to confirm menarche.

[g] At SCR, collect transfusion history for the 56 days prior to first dose of study drugs.

[h] Physical examinations, including weight, will be performed on the indicated visit days. Physical examinations on Cycle 1/Day 1 need not be repeated if previously performed within 24 hours before the first dose.

[i] Vital sign measurements will include systolic blood pressure, diastolic blood pressure, respiratory rate, pulse rate, and body temperature. They will be collected on the indicated visits, as well as at 3 hours (± 10 minutes) post-dose on Cycle 1/Day 1.

[j] Blood samples for safety laboratories (hematology and serum chemistry) will be collected on indicated visits. Creatinine clearance will be calculated at the SCR visit. The sample for safety laboratories on Cycle 1/Day 1 need not be collected if previously collected within 72 hours prior to first dose.

[k] Electrocardiograms will be performed in triplicate at pre-dose and 3 hours post-dose at the indicated visit days up to 6 cycles. The ECG should be performed within 10 minutes prior to PK sample collection. Subject should be in supine position for 5 minutes prior to each reading. Other unscheduled ECGs may be performed as clinically indicated.

[l] An ECHO/MUGA scan that was performed within 60 days before the first dose of study drugs may be used.

[m] BM samples for disease assessment and exploratory biomarkers analysis are required at SCR and pre-dose on Day 1 of Cycles 2 and 3.

[n] If subject achieves CR, CRi, or MLFS before Cycle 4/Day 1, then BMBs/BMAs will not be required on Cycle 4/Day 1. Perform BMBs/BMAs on Day 1 of Cycles 6, 9, and 12 if subject remains in CR, CRi, or MLFS. If subject does not achieve CR, CRi, or MLFS before Cycle 4/Day 1 (eg, PR on Cycle 3/Day 1), BMBs/BMAs will be required on Cycle 4/Day 1, and on Day 1 of every cycle thereafter until subject achieves CR, CRi, or MLFS. Beyond Cycle 12/Day 1, subjects who remain in CR, CRi, or MLFS on Cycle 12/Day 1 will need to undergo BMBs/BMAs on Day 1 of Cycles 18, 24, and every 6 cycles thereafter. All unscheduled BM assessments performed on non-visit days must be reported as unscheduled visits.

[o] BM samples at Screening and on Day 1 of Cycles 2, 3, 6, 9, 12, 18, 24, and every 6 cycles thereafter will be submitted for translational research. BM samples from unscheduled BMBs/BMAs should be also submitted for translational research when disease progression (relapse or progressive disease) is suspected. Additionally, submit BM samples for minimal residual disease analysis (eg, flow cytometry and/or next generation sequencing) on the day when <5% blasts in BM is observed and/or at the subsequent timepoints for BM sample collection. BM samples from other timepoints are not required to be submitted (eg, Cycle 4/Day1). Blood for exploratory biomarker analysis will be collected at the indicated timepoints in Cycle 1, and at the same timepoints as BMBs/BMAs in subsequent cycles. Refer to the Laboratory Manual for additional details and instructions.

[p] Peripheral blood collected for exploratory analysis of blasts and other pharmacodynamic circulating biomarkers at the indicated timepoints in Cycle 1, Cycle 2, and Cycle 3, and then on Day 1 of every 3-6 cycles corresponding to the timepoints for BMBs/BMAs (ie, Cycles 6, 9, 12, 18, 24, and every 6 cycles thereafter) and at EOT.

[q] Peripheral blood collected for banking plasma for future exploratory molecular analysis of biomarkers at the indicated timepoints in Cycle 1, Cycle 2, and Cycle 3, and then on Day 1 of every 3-6 cycles corresponding to the timepoints for BMBs/BMAs (ie, Cycles 6, 9, 12, 18, 24, and every 6 cycles thereafter) and at EOT.

[r] Serum will be collected from the blood obtained at the indicated timepoints for MIC-1 analysis.

[s] Informed consent specifically allowing PGx testing sample storage must be obtained before collecting sample.

[t] Quizartinib and milademetan are administered per protocol at the clinical site at the indicated visits without regard to the timing of food. Quizartinib will be dispensed for continuous qd dosing for each 28 day cycle and milademetan will be dispensed for qd dosing for 14 days of each 28 day cycle.

[u] Sparse PK samples for plasma concentrations of milademetan, quizartinib and AC886 will be collected and analyzed at pre-dose and 3 hours post-dose on the indicated visit days up to 6 cycles with time-matched ECGs. Please refer to Table 8.2 for collection schedule and other information.

[v] Study drugs and pill diary may be dispensed for at-home dosage, if regionally required.

[w] A BM re-biopsy or aspirate must be performed within 30 (± 5) days of the last dose of study drug study drug in subjects who have achieved an initial CR, CRi, MLFS, or PR to the treatment but later relapsed/developed PD while on therapy.

[x] If feasible, collect subject survival status, date and cause of death (if applicable), subsequent AML therapy, and HCT and HCT-relevant information (if performed).

Table 17.5: Schedule of Events (for the Part 2 Subgroup of 12 Subjects for DDI Substudy) – Milademetan QD 14/28 Regimen[§]

Cycle (1 cycle = 28 days)[a]	Pre-cycle		1								2						3				4 and Beyond	Post-cycle	
Visit Description	**SCR**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EX**	**EOT[b]**	**F/U[c]**
Cycle Day(s)	**−15 to −3**	**−2**	**−1**	**1**	**2**	**8**	**14**	**15**	**22**	**28**	**1**	**2**	**8**	**14**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**ND**	**ND**
Visit Window (days)						**± 2**	**± 2**		**± 2**				**± 2**			**± 2**	**± 4**				**± 4**		
Informed consent	X																						
SID number assigned	X																						
Demographics	X																						
Medical history	X																						
Inclusion/exclusion criteria	X																						
Pregnancy test[d]	X																X				X[e]	X	
FSH test[f]	X																						
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record transfusion	X[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG	X	X				X	X				X						X				X	X	
Height	X																					X	
Physical examination, including weight[h]	X	X				X	X				X						X				X	X	
Vital signs[i]	X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	
Safety laboratory[j]	X		X			X	X		X	X	X		X		X	X	X	X	X	X	X	X	
Blood for testing hepatitis B or C	X																						
Blood for testing FLT3 mutation	X																						
Triplicate ECG (12-lead)[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECHO/MUGA[l]	X																						
BM assessment	X[m]										X[m]						X[m]				X[n]		
BM for exploratory biomarker analysis[o]	X[m]										X[m]						X[m]				X[n]		

Cycle (1 cycle = 28 days)[a]	Pre-cycle		1								2						3				4 and Beyond	Post-cycle	
Visit Description	SCR	EX	EX	EX	EX	EX	EX	EX	EX	EX	EX	EX	EX	EX	EX	EX	EX	EX	EX	EX	EX	EOT[b]	F/U[c]
Cycle Day(s)	−15 to −3	−2	−1	1	2	8	14	15	22	28	1	2	8	14	15	22	1	8	15	22	1	ND	ND
Visit Window (days)						± 2	± 2		± 2				± 2			± 2	± 4				± 4		
Blood for exploratory biomarker analysis[p]			X		X	X					X						X				X	X	
Blood for banking plasma[q]			X			X					X						X				X	X	
Blood for MIC-1 analysis[r]			X		X	X	X		X		X												
PGx sample[s]			X																				
Quizartinib administration[t]				X	X	X	X	X	X	X[u]	X[u]	X	X	X[u]	X	X	X	X	X	X	X		
Milademetan administration[t]			X[u]	X	X	X	X				X[u]	X	X	X[u]			X	X			X		
Blood sample for PK[v]			X	X	X	X	X[w]	X[w]	X[w]	X	X	X	X	X	X	X	X[w]	X	X	X	X[w]	X	
Dispense quizartinib[x]					X	X		X	X			X	X		X	X	X	X	X	X	X		
Dispense milademetan[x]					X	X						X	X				X	X			X		
Pill diaries dispensed/reviewed[x]					X	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	
Medication compliance reviewed[x]						X	X		X	X			X	X	X	X	X	X	X	X	X	X	
BM re-biopsy or aspirate[y]																						X	
Follow-up survival data[z]																						X	X

AML = acute myeloid leukemia; BM = bone marrow; BMA = bone marrow aspirate; BMB = bone marrow biopsy; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS F/U = End-of-study Follow-up; EOT = End-of-treatment; EX = exam; FSH = follicle stimulating hormone; F/U = Follow-up; HCT = hematopoietic cell transplant; MUGA = multigated acquisition; ND = not determined; PD = progressive disease; PK = pharmacokinetics; SCR = Screening; SID = subject identifier.

Note: Informed consent will be obtained prior to screening procedures.

§ If RDE is determined in a different dosing schedule of milademetan than qd 14/28, the protocol will be amended to accommodate the schedule of events for Part 2 according to the RDE dosing schedule.

[a] Each cycle will last 28 days with quizartinib dosed once every day and milademetan qd on Days 1 to 14. Cohort safety assessment for dose limiting toxicities will be performed at the end of Cycle 1.

[b] End-of-treatment visit will occur within 30 days after the last administration of study drug(s). If a subject begins another anticancer therapy before the end of the 30 day period, every effort will be made to complete all of the EOT assessments prior to commencing the new therapy. If there is an abnormality in need of monitoring beyond the EOT visit, subjects will be followed until resolution or confirmed stability of the abnormality.

[c] Follow-up will occur first at 30 (± 5) days after the last dose of the study drug (this can be accomplished by a site visit or phone call if the subject cannot return to the site) and then every 3 months (± 2 weeks) until death or until Sponsor terminates study.

[d] A serum pregnancy test will be required for all female subjects of childbearing potential.

[e] Cycle 4 and beyond, a serum pregnancy test in women of childbearing potential will be required on Day 1 of every 3 cycles from Cycle 3 (ie, Cycles 6, 9, 12, etc).

[f] Obtain an FSH test in women of childbearing potential to confirm menarche.

[g] At SCR, collect transfusion history for the 56 days prior to first dose of study drugs.

[h] Physical examinations, including weight, will be performed on the indicated visit days. Physical examinations on Pre-v v'x8P t (; („xxw(„¬η(ux(Δx×xt ηκw(≥y(previously performed within 24 hours before the first dose.

[i] Vital sign measurements will include systolic blood pressure, diastolic blood pressure, res×≥Δt η–Δ (Δt ηκ5(×π'βx(Δt ηκ5(t „w(u–w (ηκ' ×xΔt ηπΔκ7((b „(P t (: (t „w(P t (1, vital signs will be measured pre-dose and 3 hours (± 10 minutes) post-dose.

[j] Blood samples for safety laboratories (hematology and serum chemistry) will be collected on indicated visits. Creatinine clearance will be calculated at the f Oe (≥β≥η7(g≤x(βt ' ×'x(y–Δ(βt yxη ('t u–Δt η–Δ≥x(β(–„(O v'x(: 8P t (: („xxw(„¬η(ux(v–''xvηκw(≥y(×Δκ ≥πβ'' (v–''xvηκw(≥η≤≥„(C; (≤–πΔs prior to first dose.

[k] Electrocardiograms will be performed in triplicate at hours 0, 1, 2, 4, and 6 on Pre-v v'x8P t (; (y–Δ(ut βx'≥„x(lt ××Δ– ≥' t ηκ'' (η≥' x-matched to the timepoints on O v'x(: 8P t (: 25(t η(×Δκ-dose, and at hours 1, 2, 4, and 6 post-w–βx(–„(O v'x(: 8P t β(: (t „w(; D(t „w(–„(O v'x(; 8P t β(: (t „w(: >7((g≤x(QOS (β≤–π'w(ux(×xΔy–Δ' xw(within 10 minutes prior to the PK sample collection. ECGs will also be collected at pre-dose and 3 hours post-dose on Days 1, 14, 15, and 22 of Cycle 1 and Day 1 of Cycles 3 to 6. Subject should be in supine position for 5 minutes prior to each reading. Other unscheduled ECGs may be performed as clinically indicated.

[l] An ECHO/MUGA scan that was performed within 60 days before the first dose of study drugs may be used.

[m] BM samples for disease assessment and exploratory biomarkers analysis are required at SCR and pre-dose on Day 1 of Cycles 2 and 3.

[n] If subject achieves CR, CRi, or MLFS before Cycle 4/Day 1, then BMBs/BMAs will not be required on Cycle 4/Day 1. Perform BMBs/BMAs on Day 1 of Cycles 6, 9, and 12 if subject remains in CR, CRi, or MLFS. If subject does not achieve CR, CRi, or MLFS before Cycle 4/Day 1 (eg, PR on Cycle 3/Day 1), BMBs/BMAs will be required on Cycle 4/Day 1, and on Day 1 of every cycle thereafter until subject achieves CR, CRi, or MLFS. Beyond Cycle 12/Day 1, subjects who remain in CR, CRi, or MLFS on Cycle 12/Day 1 will need to undergo BMBs/BMAs on Day 1 of Cycles 18, 24, and every 6 cycles thereafter. All unscheduled BM assessments performed on non-visit days must be reported as unscheduled visits.

[o] BM samples at Screening and on Day 1 of Cycles 2, 3, 6, 9, 12, 18, 24, and every 6 cycles thereafter will be submitted for translational research. BM samples from unscheduled BMBs/BMAs should be also submitted for translational research when disease progression (relapse or progressive disease) is suspected. Additionally, submit BM samples for minimal residual disease analysis (eg, flow cytometry and/or next generation sequencing) on the day when <5% blasts in BM is observed and/or at the subsequent timepoints for BM sample collection. BM samples from other timepoints are not required to be submitted (eg, Cycle 4/Day1). Blood for exploratory biomarker analysis will be collected at the indicated timepoints in Cycle 1, and at the same timepoints as BMBs/BMAs in subsequent cycles. Refer to the Laboratory Manual for additional details and instructions.

[p] Peripheral blood collected for exploratory analysis of blasts and other pharmacodynamic circulating biomarkers at the indicated timepoints in Cycle 1, Cycle 2, and Cycle 3, and then on Day 1 of every 3-6 cycles corresponding to the timepoints for BMBs/BMAs (ie, Cycles 6, 9, 12, 18, 24, and every 6 cycles thereafter) and at EOT.

[q] Peripheral blood collected for banking plasma for future exploratory molecular analysis of biomarkers at the indicated timepoints in Cycle 1, Cycle 2, and Cycle 3, and then on Day 1 of every 3-6 cycles corresponding to the timepoints for BMBs/BMAs (ie, Cycles 6, 9, 12, 18, 24, and every 6 cycles thereafter) and at EOT.

[r] Serum will be collected from the blood obtained at the indicated timepoints for MIC-1 analysis.

[s] Informed consent specifically allowing PGx testing sample storage must be obtained before collecting sample.

[t] Quizartinib and milademetan are administered per protocol at the clinical site at the indicated time without regard to the timing of food, except where noted.

[u] Quizartinib and milademetan will be dosed on an empty stomach (no food for at least 2 hours pre-w–βx2(–„(O v’x(: 8P t (: 5(O v’x(: 8P t (; D5(O v’x 2/Day 1, and Cycle 2/Day 14. Subjects will also be required to fast for 2 additional hours post-dose.

[v] PK samples for milademetan, quizartinib and AC886 are collected on the indicated timepoints. PK samples will be collected at pre-dose and at 0.5, 1, 2, 3, 4, 6, and 8 hours post-w–βx(–„(P t β(: (t „w(; D(–y(O v’x(: (t „w(–„(P t β(: (t „w(: >(–y(O v’x(; 5(t η(×Δx-dose and 3 hour post-dose on Days 1, 14, 15, and 22 of Cycle 1 and on Day 1 of Cycles 3 to 6, and at pre-dose at all other indicated visit days. Please also refer to Table 8.3 for collection schedule and other information.

[w] Indicates that milademetan and/or quizartinib and AC886 PK samples at pre-dose and 3 hours post-dose will be collected on Days 14, 15 and 22 of Cycle 1 and Day 1 of Cycles 3 to 6.

[x] Study drugs and pill diary may be dispensed for at-home dosage, if regionally required.

[y] A BM re-biopsy or aspirate must be performed within 30 (± 5) days of the last dose of study drug in subjects who have achieved an initial CR, CRi, MLFS, or PR to the treatment but later relapsed/developed PD while on therapy.

[z] If feasible, collect subject survival status, date and cause of death (if applicable), subsequent AML therapy, and HCT and HCT-relevant information (if performed).

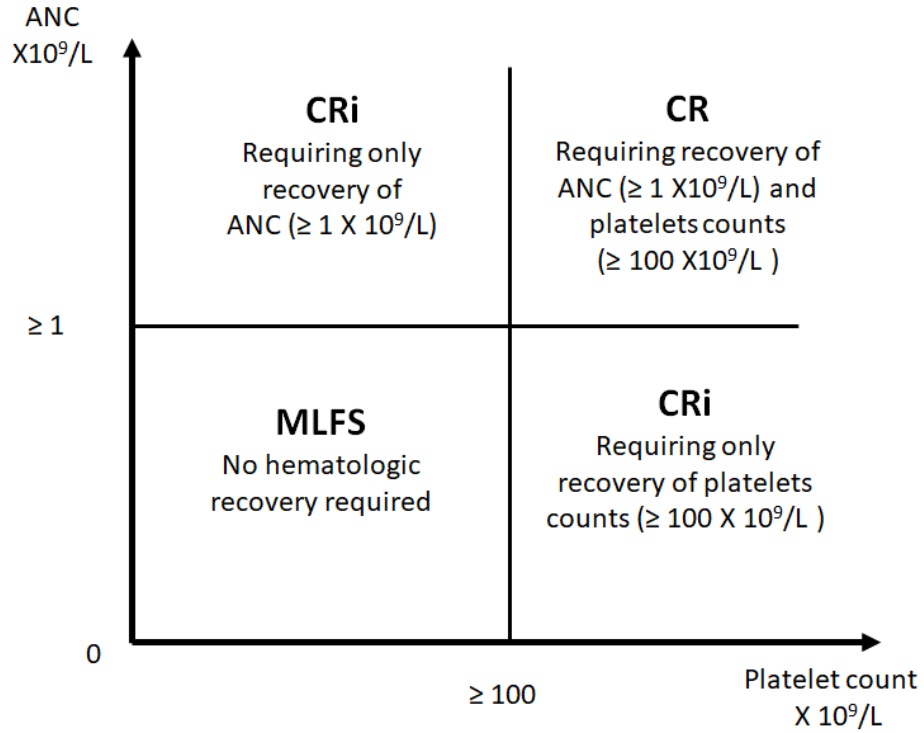
17.4. Response Criteria for AML[19]

Category	Definition
Complete Remission (CR)	Bone marrow blasts <5% Absence of circulating blasts and blasts with Auer rods Absence of extra-medullary disease Au β–’πηκ(„xπηΔ–×≤³ϒ(v–π„,η(lMa O2(: 7Θ × 10^9/L P’ι ηκ’χη(v–π„,η(: 99 × 10^9/L
CR with Incomplete Blood Count Recovery (CRi) (Figure 17.1)	All CR criteria except for residual neutropenia (ANC <1.0 × 10^9/L) or thrombocytopenia (platelet count <100 × 10^9/L)
Morphologic Leukemia-free State (MLFS)	Bone marrow blasts <5% Absence of blasts with Auer rods Absence of extramedullary disease No hematologic recovery required ○ **Note**: Mt ΔΔ– (β≤–π’ϑ„,–η(’ xΔx” (ux(t ×’ι βη≥v Ω(t η(’χt βη(200 cells should be enumerated or cellularity should be at least 10%
Partial Remission (PR)	Decrease of bone marrow blast percentage by at least 50% to a value of 5% to 25% All hematologic criteria of CR: ○ Ma O(: 7Θ((: 9^9/L ○ ×’ι ηκ’χη(v–π„,η(: 99((: 9^9/L
Stable Disease (SD)	Absence of CR, CRi, MLFS, or PR, and criteria for PD not met ○ **Note**: SD can be reported as each assessment not persisting for 3 months, whereas SD which persists for at least 3 months will be summarized for the efficacy analysis.
Relapse (after CR or CRi)	Bone marrow blasts A 5(–Δ Reappearance of leukemic blasts in the peripheral blood, or Development of extramedullary disease

Category	Definition
Progressive Disease (PD)	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in ANC to an absolute level of >0.5 × 10^9/L, and/or platelet count to >50 × 10^9/L (non-transfused); or >50% increase in peripheral blasts (WBC × % blasts) to >25 × 10^9/L (in the absence of differentiation syndrome); or New extra-medullary disease

ANC = absolute neutrophil count; WBC = white blood cells

Figure 17.1: Hematologic Recovery Requirements for CR and CRi



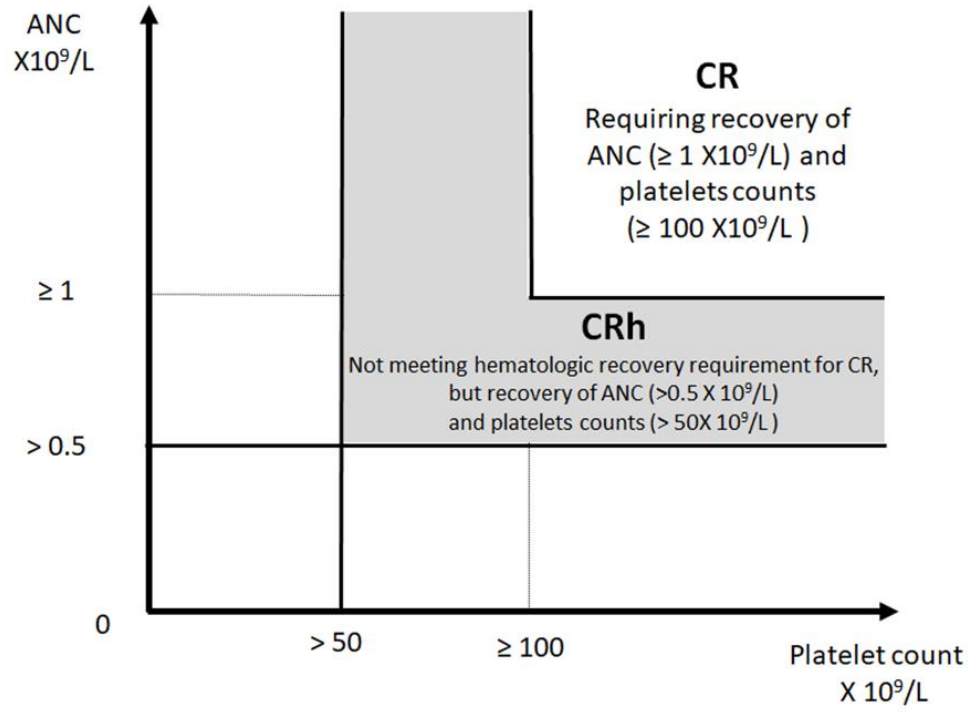
ANC = absolute neutrophil count; CR = complete remission; CRi = CR with incomplete blood count recovery; MLFS = morphologic leukemia-free state

17.5. Additional Definitions/Response Criteria

CRh evaluation will be conducted separately from those in Section 17.4.

Category	Definition
CR with Partial Hematological Recovery (CRh)[28] (Figure 17.2)	All CR criteria except for hematologic recovery BUT partial hematological recovery (ANC >0.5 × 10^9/L **and** platelet count >50 × 10^9/L) were observed.

Figure 17.2: Hematologic Recovery Requirements for CR and CRh



ANC = absolute neutrophil count; CR = complete remission; CRi = CR with incomplete blood count recovery

17.6. Prohibited Concomitant Medications

Potential QT/QTc Prolonging Drugs

The following list describes medications which prolong QTc interval and are prohibited during treatment with quizartinib and milademetan combination.

This list should not be considered all-inclusive. Consult individual drug labels for specific ≥„y–Δ‘ t ηΣ–„,(–„,(t (wΔπz β(×Δ–×x„,β≥η (η–(×Δ–”–„z(d g v(≥„ηχΔ t ”7

Note: Exceptions are made for antibiotics and antifungals that are used as standard of care for the prevention or treatment of infections or if the Investigator believes that beginning therapy with a potentially QTc-prolonging medication is vital to an individual βπu–xvη β care while on study (Section 5.6.2).

Known QT/QTc-Prolonging Drugs	Generic Drug Name
Macrolide antibiotics	azithromycin erythromycin clarithromycin roxithromycin
Fluoroquinolone antibacterials	moxifloxacin ciprofloxacin gatifloxacin grepafloxacin levofloxacin sparfloxacin
Azole antifungals	fluconazole
Antimalarials	chloroquine halofantrine quinidine
Antiprotozoals	pentamidine
Antiemetics, gastrokinetics	droperidol ondansetron cisapride domperidone
Anticancer	aclarubicin arsenic trioxide oxaliplatin vandetanib

Known QT/QTc-Prolonging Drugs	Generic Drug Name
Antipsychotics, antidepressants, anesthetics, and other CNS agents	chlorpromazine cocaine citalopram donepezil escitalopram haloperidol ibogaine levomepromazine levomethadyl acetate levosulpiride methadone mesoridazine pimozide propofol sevoflurane sulpiride sultopride thioridazine
Antiplatelet agents	anagrelide cilostazol
Antihistamines	astemizole terfenadine
Antiarrhythmics, antihypertensives, antihyperlipidemics	amiodarone bepridil disopyramide dofetilide dronedarone flecainide ibutilide papaverine HCl probucol procainamide sotalol terlipressin terodiline

Adapted from: https://www.crediblemeds.org/pdftemp/pdf/CombinedList.pdf (site list last revised 17 Feb 2019).

The following list describes non-QT-prolonging medications that may be administered to manage nausea and vomiting. This list should not be considered all-inclusive.

Antiemetics (Non-QT-prolonging)[15]
aprepitant
droperidol
fosaprepitant
metoclopramide

The following list describes medications which are strong inducers of CYP3A and are prohibited during treatment with quizartinib and milademetan combination. This list should not be considered all-inclusive.

Strong CYP3A Inducers
avasimibe
carbamazepine
phenytoin
rifampin
f ηζ(V-≤, βζj −Δη
enzalutamide
mitotane

Adapted from: https://www.druginteractioninfo.org

17.7. Highly Effective Methods of Birth Control

Per the guidance from the Clinical Trial Facilitation Group (CTFG) of the European Heads of Medicines Agencies (HMA),[29] 66 methods that can achieve a failure rate of less 1% per year when used consistently and correctly are considered as highly effective birth control methods. Per the guidance, such methods include:

Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation including oral, intravaginal and transdermal formulations

Progestogen-only hormonal contraception associated with inhibition of ovulation, including oral, injectable and implantable formulations

Intrauterine device (IUD)

Intrauterine hormone-releasing system (IUS)

Bilateral tubal occlusion

Vasectomized partner (provided that the partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success)

Complete sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.)

Prior to starting quizartinib/placebo, the Investigator will discuss highly effective methods of birth control as defined above with women of childbearing potential (as defined in Section 4.1) and men who are not surgically sterile.

17.8. FLT3-ITD Mutation Assay

Of note, a companion diagnostic is being developed by Navigate for the US and European Union 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 internal tandem duplication (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.

This test is approved by the FDA for investigational use and is Conformité Européenne (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.

17.9. Eastern Cooperative Oncology Group (ECOG) Performance Status

The following table summarizes the ECOG Performance Status Scale.[30]

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work)
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

17.10. New York Heart Association (NYHA) Functional Classification

The following table lists the NYHA Classes of Heart Failure.[31]

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.