CLINICAL STUDY PROTOCOL

A PHASE 1 STUDY OF MILADEMETAN (DS-3032b), AN ORAL MDM2 INHIBITOR, IN DOSE ESCALATION AS A SINGLE AGENT AND IN DOSE ESCALATION/EXPANSION IN COMBINATION WITH 5-AZACITIDINE IN SUBJECTS WITH ACUTE MYELOGENOUS LEUKEMIA (AML) OR HIGH-RISK MYELODYSPLASTIC SYNDROME (MDS)

DS3032-A-U102

IND NUMBER: 118125

VERSION 5.0, 06 Mar 2020

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INVESTIGATOR AGREEMENT

A PHASE 1 STUDY OF MILADEMETAN (DS-3032b), AN ORAL MDM2 INHIBITOR, IN DOSE ESCALATION AS A SINGLE AGENT AND IN DOSE ESCALATION/EXPANSION IN COMBINATION WITH 5-AZACITIDINE IN SUBJECTS WITH ACUTE MYELOGENOUS LEUKEMIA (AML) OR HIGH-RISK MYELODYSPLASTIC SYNDROME (MDS)

Sponsor Approval:

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

PPD	PPD
Print Name	**Signature**
Senior Director, Global Oncology Research and Development	06 Mar 2020
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

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

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

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International 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)**

DOCUMENT HISTORY

Version Number	Version Date
4.0	21 Oct 2019
3.0	10 May 2018
2.0	24 Aug 2017
1.0	30 May 2014

SUMMARY OF CHANGES

Amendment Rationale:

The main purpose of this amendment is to clarify subject visits for assessments and sample collections in the alternative (5+2) AZA dosing schedule.

Changes to the Protocol:

Please refer to the comparison document for protocol Version 5.0 (dated 06 Mar 2020) versus protocol Version 4.0 (dated 21 Oct 2019) for actual changes in-text. The summary of changes below is a top-line summary of major changes in the DS3032-A-U102 clinical study protocol (Version 5.0) by section.

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

Section # and Title	Description of Change	Brief Rationale
Protocol Synopsis (Study Design - Part 1A [Dose escalation of milademetan in combination with AZA]) Section 3.1.2.2. Part 1A (Dose Escalation of Milademetan in Combination with AZA) Figure 3.2 Dosing Schedule of Milademetan in Combination with 5-Azacitidine Figure 3.3 Alternative 5 Azacitidine Dosing Schedule in Combination with Milademetan at RDE Section 5.1.4 Administration	Updated/added language regarding the alternative schedule and when the dosing schedules may be evaluated.	Clarification
Section 3.1.3 Part 2 (Dose Expansion of Milademetan in Combination with AZA)	Added statement, "If the safety and efficacy data from the '1 to 7' and '5+2' schedules of AZA are comparable in the Dose Escalation, both AZA schedules will be allowed in Dose Expansion."	Clarification
Section 6.4.3 Blood Sample for Banking Plasma Table 17.2: Schedule of Events Part 1A (Dose Escalation) and Part 2 (Dose Expansion) – with	Added that assessments/sample collection for Cycle 1/Day 7 will be done on Day 8 and Day 14 will be done on Day 15, for subjects on the alternative (5+2)	Clarified the subject visits for assessments and sample collections" in the alternative (5+2) dosing schedule, in combination with

Section # and Title	Description of Change	Brief Rationale
Milademetan on Days 5 to 14 (Schedule E) – footnotes e, t and v Table 17.3: Schedule of Events Part 1A (Dose Escalation) and Part 2 (Dose Expansion) – with Milademetan on Days 8 to 14 (Schedule F) – footnote e and t	AZA schedule Table 17.2 Added footnote 'e' to Cycle 1/Day 14, Cycle 2/Days 5-7, Cycle 3/Days 5-7, and Cycle 4+/Days 5-7 Table 17.3 Added footnote 'e' to Cycle 1/Day 14, Cycle 2/Day 7, Cycle 3/Day 7, and Cycle 4+/Day 7	milademetan at RDE (only at the RDE dose and dose schedule) to provide an alternative schedule for sites that are not open on the weekends or subjects who cannot come to the study site on the weekends.
Table 8.1 Cycle 1 Blood Sample Collection for Pharmacokinetics During Dose Escalation (Part 1A, Schedule E) Table 8.2: Cycle 1 Blood Sample Collection for Pharmacokinetics During Dose Escalation (Part 1A, Schedule F) Table 8.4: Cycle 1 Sparse Sample Collection for Milademetan Pharmacokinetics During Dose Expansion for All Subjects Section 11.5.1 Pharmacokinetic Analyses	Added that PK samples will not be collected for subjects on the alternative (5+2) AZA schedule	Clarification
Section 11.10. Sample Size Determination	Added 'evaluable' to the paragraph discussing "Dose Escalation (Part 1 and Part 1A)."	Clarification
Section 15.3.1.3 Sponsor's Clinical Study Manager/Delivery Lead Section 15.3.1.5 Sponsor's Biostatistician	Revised study member information	Update due to changes in team members
Table 17.2: Schedule of Events Part 1A (Dose Escalation) and Part 2 (Dose Expansion) – with Milademetan on Days 5 to 14 (Schedule E)	Separated out blood sample collection for PK of milademetan and AZA Moved MIC-1 serum sample from Cycle 1/Day 5 0.5 hours to Pre-dose Footnote p - deleted "The bone marrow sample on Cycle 1/Day 5 is optional."	Clarification/correction
Table 17.3: Schedule of Events Part 1A (Dose Escalation) and Part 2 (Dose Expansion) – with Milademetan on Days 8 to 14 (Schedule F)	Deleted MIC-1 serum sample from Cycle 2 Days 1-6 and Day 7 Footnote o - deleted "A bone marrow sample on Cycle 1/Day 8 is optional.	Correction

PROTOCOL SYNOPSIS

IND Number:	118125
Protocol Number:	DS3032-A-U102
Investigational Products:	Milademetan (DS-3032b) 5-Azacitidine (AZA) (for combination treatment with milademetan)
Active Ingredient(s)/INN:	Milademetan (3'*R*,4'*S*,5'*R*)-*N*-[(3*R*,6*S*)-6-Carbamoyltetrahydro-2*H*-pyran-3-yl]-6''-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2''-oxo-1'',2''-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3''-indole]-5'-carboxamide mono(4-methylbenzenesulfonate) monohydrate AZA 4-amino-1-β-D-ribofuranosyl-s-triazin-2(1H)-one
Study Title:	A Phase 1 Study of Milademetan (DS-3032b), an Oral MDM2 Inhibitor, in Dose Escalation as a Single Agent and in Dose Escalation/Expansion in Combination with 5-Azacitidine in Subjects with Acute Myelogenous Leukemia (AML) or High-Risk Myelodysplastic Syndrome (MDS)
Study Phase:	Phase 1
Indication Studied:	Milademetan will be evaluated in subjects with relapsed or refractory (R/R) AML or high-risk MDS in Parts 1 and 1A (Dose Escalation), and R/R AML, newly diagnosed AML unfit for intensive chemotherapy, or high-risk MDS in Part 2 (Dose Expansion).
Study Objectives:	**Study Objectives** **Primary Objectives** Part 1 and Part 1A • To assess the safety and tolerability of milademetan as a single agent (Part 1) and in combination with AZA (Part 1A). • To determine the maximum tolerated dose (MTD) of milademetan as single agent and in combination with AZA and to identify a recommended dose for an expansion cohort (RDE) of milademetan plus AZA. Part 2

- To confirm the safety and tolerability of milademetan in combination with AZA at the RDE and identify the recommended Phase 2 dose (RP2D).
- To evaluate the efficacy of milademetan in combination with AZA in subjects with AML or high-risk MDS.

Secondary Objectives

Part 1 and Part 1A

- To evaluate the pharmacokinetics (PK) of milademetan following single and multiple dosing.

Part 2

- To evaluate the PK of milademetan at the RDE.

Outcome Measures

Primary Outcome Measures

Part 1 and Part 1A

1. Number of subjects with DLTs by the end of the Dose Escalation part (timeframe: within 5 years of first subject enrolled).

Part 1, Part 1A, and Part 2

1. Number of subjects with treatment-emergent adverse events (TEAEs) (timeframe: within 6 years of first subject enrolled).

Part 2

1. Number of subjects who achieved CR, CRi or MLFS for AML and who attained CR, marrow CR (mCR) or PR for high-risk MDS as the best response (timeframe: within 6 years of first subject enrolled).

Secondary Outcome Measures

Part 1, Part 1A, and Part 2

- Plasma concentrations and PK parameters of milademetan (timeframe: within 6 years of first subject enrolled).

Study Design:	This will be a Phase 1, open-label study of milademetan as a single agent (Part 1) and in combination with AZA (Part 1A) to assess its safety and tolerability and identify the MTD and RDE (in Dose Escalation) in subjects with R/R AML or high-risk MDS and to confirm the safety and tolerability of RDE and identify a RP2D (in Dose Expansion [Part 2]) in subjects with R/R AML, newly diagnosed AML unfit for intensive chemotherapy, or high-risk MDS.

Dose regimen

In Part 1, milademetan will be administered once daily (QD) on Days 1 to 21 of a 28-day cycle (qd 21/28) in cohorts of increasing doses, starting from 60 mg (Schedule a). Alternative, less frequent, drug administration schedules of qd on Days 1 to 7 of a 28-day cycle (qd 7/28) (Schedule b), qd for 3 of 14 days repeated twice in a 28-day cycle (qd 3/14 × 2) (Schedule c), and qd on Days 1 to 14 of a 28-day cycle (qd 14/28) (Schedule d) will also be evaluated in Dose Escalation, starting from the MTD determined in the qd 21/28 schedule.

The dosing schedules for the dose escalation in Part 1A in combination with AZA will be identified based on safety, PK, PDy, and clinical response data collected during dose escalation of milademetan as a single agent and reviewed by the Principal Investigators and Sponsor.

Part 1 (Dose escalation of milademetan single agent)

Dose escalation of milademetan to determine the MTD will be guided by a Bayesian logistic regression model (BLRM) following escalation with overdose control (EWOC) principle with a starting dose of 60 mg based on safety and tolerability data obtained in the solid tumor or lymphoma first-in-human study of milademetan (Study DS3032-A-U101).

Dose level increment during Dose Escalation by BLRM with EWOC

The dose increments for milademetan guided by BLRM with EWOC will also adhere to the following restrictions:

- The dose level increment should be no less than 30% in order to have distinction among dose levels considering the inter-subject variability in exposure, but flexibility may be applied in selecting the dose to accommodate the available dosage form strengths.
- The dose level increment should be no more than 100% even if the model suggests a higher dose than 100% for the next cohort.
- In the event of a dose-limiting toxicity (DLT), the next 2 subjects in the current cohort will receive milademetan treatment starting at least 1 week apart.

Cohorts of 3 to 6 subjects will be enrolled and assessed for DLTs before escalation to a new higher dose. If 2 evaluable subjects in a cohort experience a DLT before the enrollment of the next subject, the model will be re-evaluated before enrollment of any additional subjects to the cohort. Enrollment of subjects to a new cohort

requires completion of DLT evaluation of at least 3 subjects treated in the current cohort. Subjects who have neither completed a DLT evaluation nor experienced a DLT will be censored and not included in the BLRM update. In the event that subjects in the previous cohort experience a DLT after the enrollment of subjects to a new cohort has begun, 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 doses.

For a subject to be considered evaluable for dose escalation decisions, the subject must have received at least 75% of the doses during Cycle 1 or experienced a DLT in Cycle 1. The final MTD will be decided based on considerations of the respective MTD estimated by the BLRM and on an overall assessment of safety data from subsequent cycles and PK/PDy information collected at all doses tested. For dose determination, the following stopping rules will be implemented for the Dose Escalation part: (a) at least 6 evaluable subjects have been enrolled at the MTD level with at least 18 evaluable subjects in total enrolled in the Dose Escalation part, (b) at least 9 evaluable subjects have been enrolled at a dose level which is the model's recommendation for the next dose cohort and for which the posterior probability of targeted toxicity is at least 50%, or (c) dose level -1 is too toxic.

Additional subjects for the characterization of safety, PK, or PDy may be added to 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.

The same dose escalation method applies to the other dosing schedules of milademetan as a single agent and in combination with AZA (Part 1A).

<u>Dose escalation using alternative single agent milademetan drug administration schedule</u>

Based on safety, PK, and PDy data collected during Dose Escalation using the qd 21/28 schedule of milademetan over 5 dose levels and reviewed by the Principal Investigators and Sponsor, alternative, less frequent dosing schedules were evaluated for dose escalation. Starting from the MTD dose level (160 mg) established for the qd 21/28 schedule, dose escalation using the following recommended alternative dosing schedules were performed in lieu of the qd 21/28 schedule allowing parallel evaluation:

- qd 7/28 schedule (Schedule b)
- qd 3/14 × 2 schedule (Schedule c)

- qd 14/28 schedule (Schedule d)

Note: After the finalization of Version 3.0 of this protocol on 10 May 2018, Study DS-3032-A-U102 completed enrollment in Part 1, which evaluated milademetan as a single agent therapy in 4 different dose schedules (Schedules a to d). Although no DLTs were observed in the single cohorts of 160 mg schedules b (qd 7/28) and c (qd 3/14 × 2), respectively, neither schedule was able to control leukemia and neither was pursued further. In Schedule d (qd 14/28), when the dose was escalated from 160 mg with no DLTs in 3 subjects to the next higher dose of 220 mg, DLTs based on Grade 3 nausea were observed in the first 2 subjects. The dose was therefore de-escalated to 160 mg. However, no further enrollment was pursued at 160 mg in this dose schedule since the dose was same as the MTD determined in the more frequent dose schedule (Schedule a; qd 21/28).

Part 1A (Dose escalation of milademetan in combination with AZA)

In Part 1A, subjects will be treated with AZA at 75 mg/m^2 subcutaneously (SQ) or intravenously (IV) in combination with escalating doses of milademetan. Two dosing schedules for milademetan will be evaluated. In Schedule e, AZA will be administered on Days 1 to 7 and milademetan will be administered qd on Days 5 to 14 (with an overlap of both drugs administered on Days 5 to 7) in each 28-day cycle. In Schedule f, AZA will be administered on Days 1 to 7 and milademetan will be administered qd on Days 8 to 14 (sequential treatment) in each 28-day cycle. After the RDE (ie, the optimal dose and schedule of milademetan) is identified, an alternative schedule of AZA will be tested in combination with milademetan at RDE (only at the RDE dose and dose schedule). Instead of the 7-day consecutive administration from Days 1 to 7, AZA will be administered on Days 1 to 5 and then from Days 8 to 9 ("5+2"), with AZA dosing interruption during the weekend (eg, for logistic challenges such as closure of study sites or investigational pharmacy during the weekend). Both of the dosing schedules of milademetan (schedules e and f) may be evaluated in parallel during dose escalation. The starting dose for milademetan in combination with AZA will be 160 mg (the MTD of single agent milademetan treatment in the qd 21/28 schedule) and will follow dose escalation per the BLRM with the EWOC principle.

Subjects should avoid a strong CYP3A4 inhibitors while entering the study. However, if a subject has a medical condition which the Investigator believes is best treated by a strong CYP3A4 inhibitor, the strong CYP3A4 inhibitor can be introduced and the milademetan dose will be reduced by 50%. No dose modification for AZA is required with the concomitant administration of a strong CYP3A

inhibitor.

Milademetan can be administered without regards to the timing of food (except for subjects in Part 1, who were required to avoid food for 2 hours before and 1 hour after milademetan administration). If the dose of 160 mg (80 mg for subjects receiving a strong CYP3A4 inhibitor) is not well tolerated, then a lower dose of 120 mg (60 mg for subjects receiving a strong CYP3A4 inhibitor) will be evaluated. Both of the dosing schedules may be evaluated in parallel.

Dose-limiting toxicity definition

A DLT is defined as any TEAE not attributable to disease or disease-related processes that occurs during the observation period (Cycle 1) in each dose-level cohort and is Grade 3 or higher according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (Version 4.03 before 01 Apr 2018), with the exceptions as defined below.

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

- Grade ≥3 aspartate aminotransferase (AST)/alanine aminotransferase (ALT) levels lasting >3 days.
- AST/ALT >5 × ULN if accompanied by ≥Grade 2 elevation in bilirubin.

The following events are classified as DLTs:

- Subjects who are unable to complete at least 75% of the prescribed dose of milademetan or AZA in Cycle 1 as a result of non-disease-related Grade ≥2 events will be considered to have a DLT.
- Persistent bone marrow aplasia in the absence of malignant cell infiltration, per institutional guidelines, and failure to recover a peripheral absolute neutrophil count $\geq 0.5 \times 10^9$/L and platelets $\geq 20 \times 10^9$/L while withholding study drug, resulting in a >2-week delay in initiating Cycle 2.

The following adverse events (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 therapeutic antiemetic agents for managing established nausea or vomiting.
- Grade 3 diarrhea that has resolved to Grade ≤2 within 48 hours after standard antidiarrheal therapies.

	• Isolated laboratory findings not associated with signs or symptoms including Grade 3/4 alkaline phosphatase, uric acid, amylase, and lipase elevations, and Grade 3 hyponatremia lasting <72 hours developed from Grade 1 at baseline. • Due to the nature of AML and MDS, significant abnormalities of hematological parameters are expected from the underlying disease or as part of anticancer therapy. Therefore, no hematological DLTs are defined for this protocol. • Alopecia. • Grade ≥3 electrolyte abnormalities that are corrected to ≤Grade 1 within 24 hours. **Part 2 (Dose Expansion)** Upon completion of Part 1 and Part 1A with established RDE and drug administration schedule, the Dose Expansion part will begin to confirm the safety and tolerability of milademetan in combination with AZA, to determine the PDy in blood and/or bone marrow biopsies/aspirates, and to evaluate preliminary efficacy and identify the RP2D. Three cohorts of approximately 40 subjects per cohort with AML or high-risk MDS will be concurrently enrolled and treated in Dose Expansion (total of approximately 120 subjects) as follows: 1. Cohort 1: Subjects with R/R AML. 2. Cohort 2: Subjects with newly diagnosed AML and are unfit for intensive chemotherapy. 3. Cohort 3: Subjects with high-risk MDS. **Note**: For Cohorts 1 and 3 of Part 2 (Dose Expansion), more stringent eligibility criteria regarding prior AML or MDS therapies will be applied in order to create a more homogenous subject population (as noted in the Subject Eligibility Criteria section below).
Study Duration:	The study duration is expected to last approximately 6 years from the time the first subject is enrolled in Part 1 of the study. The number of treatment cycles is not fixed in this study. 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.
Study Sites and Location:	Approximately 12 US sites are planned for Part 1 and Part 1A (Dose Escalation).

	Approximately 12 US sites are planned for Part 2 (Dose Expansion).
Planned Sample Size:	The Dose Escalation parts of this study (Part 1 and Part 1A) will follow a BLRM + EWOC design with at least 3 DLT-evaluable subjects per dose level. In Dose Escalation Parts 1 and 1A, approximately 80 subjects may be enrolled to estimate the MTDs of milademetan as a single agent and in combination with AZA and to identify RDE. The Dose Expansion part (Part 2) will enroll subjects in the following 3 cohorts: (1) R/R AML (approximately 41 subjects), (2) newly diagnosed AML unfit for intensive chemotherapy (approximately 39 subjects), or (3) high-risk MDS (approximately 39 subjects).
Subject Eligibility Criteria:	**Inclusion Criteria (Part 1/1A and Part 2)** 1. Subjects with histological confirmation of primary or secondary AML according to the 2016 World Health Organization criteria classification, or high-risk MDS (defined by Revised International Prognostic Scoring System score of High or Very High. • Part 1 and 1A (Dose Escalation) o Subjects with R/R (R/R) AML, OR o Subjects with untreated, high-risk MDS or subjects who have received prior MDS treatment regimens. o Subjects ≥18 years old. **Note**: There is no minimum or maximum number of prior AML or MDS treatment regimens for Part 1 and 1A. • Part 2 (Dose Expansion) o Cohort 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 • Subjects have received 1 to 3 prior treatment regimens for AML if prior treatments included an intensive chemotherapy (eg, anthracycline-based therapy and/or intermediate or high dose of cytarabine), OR Subjects who have received 1 to 2 prior treatment regimens for AML if prior treatments did not include an intensive

chemotherapy.

- Subjects ≥18 years old.

- Cohort 2: Newly diagnosed AML
  - Subjects with newly diagnosed AML who are ineligible for intensive induction chemotherapy (eg, combination of an anthracycline and cytarabine). Subjects must have had no prior AML treatment, with the exceptions of therapy for antecedent hematologic malignancies (eg, azacitidine for MDS) or hydroxyurea.
  - Subjects ≥75 years old, OR

    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, or 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.
- Cohort 3: High-risk MDS
  - Subjects with untreated, high-risk MDS or who received up to 2 prior MDS treatment regimens. Prior MDS therapy here excludes supportive care such as transfusion, or erythropoiesis-stimulating agent.

2. Has an Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.
   - As an exception, subjects with newly diagnosed AML between 18 and 74 years old (inclusive) in Part 2 Cohort 2

with ECOG Performance Status of 3 will be eligible.

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 creatinine clearance 50-60 mL/min AND has serum creatinine ≤1.5 × ULN. In obese subjects, the lean body weight can be used in the equation instead of actual body weight.
4. Has adequate hepatic function, defined as:
   - AST/ALT ≤2.5 × ULN (≤5 × ULN if deemed elevated due to leukemia), and
   - Serum total bilirubin ≤1.5 × ULN (≤3 × ULN if deemed elevated due to leukemia or in subjects with documented Gilbert's Syndrome).
5. Subject (or legally acceptable representative) is able to provide written informed consent, comply with protocol visits and procedures, and take oral medication, and does not have any active infection or comorbidity that would interfere with therapy.
6. 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).

   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.
7. Subject must be fully informed about their illness and the investigational nature of the study protocol (including foreseeable risks and possible side effects).
8. Subject must sign and date an Institutional Review Board-approved informed consent form (including Health Insurance Portability and Accountability Act authorization, if applicable) before performance of any study-specific procedures or tests.
9. Able and willing to provide bone marrow biopsies/aspirates as

requested by the protocol.

10. Is willing to undergo malignancy genotyping for TP53 mutation, insertion, or deletion at Screening.

Exclusion Criteria

1. Has a diagnosis of acute promyelocytic leukemia.
2. Has a malignancy that is known to contain a non-synonymous mutation, insertion, or deletion in the TP53 gene determined previously or at Screening.
3. 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.
4. Has other concurrent primary malignancy that required systemic anti-neoplastic treatment within the previous 2 years, except for localized cancers that have apparently been cured, such as non-melanoma skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast.
5. Any condition that would preclude adequate absorption of milademetan, including refractory nausea and vomiting, malabsorption, biliary shunt, significant bowel resection, and/or graft-versus-host disease (GVHD) affecting the gut.
6. Has an uncontrolled infection requiring IV antibiotics, antivirals, or antifungals.
7. Has known human immunodeficiency virus infection with evidence of active infection by HIV RNA viral load, or active hepatitis B or C infection based on positive tests during Screening.
8. Has a concomitant medical condition that would increase the risk of toxicity.
9. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to NCI-CTCAE Grade ≤1, or baseline. Subjects with chronic Grade 2 toxicities may be eligible per discretion of the Investigator and Sponsor (eg, Grade 2 chemotherapy-induced neuropathy).
10. Has received hematopoietic cell transplantation (HCT) within 60 days of the first dose of study drugs.

11. Clinically significant 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.
12. Is receiving concomitant treatment with a strong inducer of cytochrome P450 3A4/5 or consumption of St. John's Wort (hypericin) within 3 days prior to the first dose and during treatment.
13. Received anti-AML therapy (except for hydroxyurea) or anti-MDS therapy 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.
    - Hydroxyurea must be discontinued at least 48 hours prior to study treatment.
14. Had major surgery within 4 weeks prior to study drug treatment.
15. Participated in a therapeutic clinical study within a washout time of 2 weeks or 5 half-lives of the drug/biologic (whichever is longer) before starting study drug treatment under this protocol, or current participation in other therapeutic investigational procedures.
16. Uncontrolled or significant cardiovascular disease, including:
    a. Prolongation of corrected QT interval using Fridericia's method (QTcF) at rest, where the mean QTcF interval is >480 ms based on triplicate electrocardiograms (ECGs).
    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. NYHA Class III or IV congestive heart failure. i. Known LVEF ≤50% or institutional lower limit of normal. • As an exception, subjects with newly diagnosed AML between 18 and 74 years old in Part 2 Cohort 2 with LVEF ≤50% or institutional lower limit of normal will be eligible. j. Uncontrolled hypertension. k. Left bundle branch block. 17. Known DLCO ≤65% or FEV1 ≤65%. • As an exception, subjects with newly diagnosed AML between 18 and 74 years old in Part 2 Cohort 2 with DLCO ≤65% or FEV1 ≤65% will be eligible. 18. Pregnant or breastfeeding. 19. Substance abuse or medical, psychological, or social conditions that, in the opinion of the Investigator, may interfere with the subject's participation in the clinical study or evaluation of the clinical study results. 20. Prior treatment with an MDM2 inhibitor.
Dosage Form, Dose, and Route of Administration:	Milademetan will be administered as a single oral capsule or as a combination of multiple oral capsules containing 5 mg, 20 mg, 80 mg, and/or 200 mg milademetan, which will be individually packaged in desiccant-embedded aluminum blisters, and 30 mg, 80 mg, and/or 100 mg capsules that are packaged in high density polyethylene bottles. AZA will be administered at 75 mg/m^2 SQ or IV in combination with milademetan in the selected dosing schedule. AZA is commercially available as a lyophilized powder in 100 mg single-dose vials, packaged in cartons of 1 vial, to be reconstituted in sterile water for use according to the package insert.
Study Endpoints:	**Safety Endpoint** Safety is the primary endpoint and 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 ECG parameters (including QTcF). Adverse events will be categorized

	using Medical Dictionary for Regulatory Activities (MedDRA) Version 17.0. Adverse events and laboratory test results will be graded according to the NCI-CTCAE Version 5.0 (Version 4.03 before 01 Apr 2018). **Pharmacokinetic and Pharmacodynamic Endpoints** The PK parameters for milademetan will include maximum plasma concentration (Cmax), time to reach maximum plasma concentration (Tmax), trough plasma concentration (Ctrough), and area under the plasma concentration-time curve up to time 24 hours (AUC24h). In addition, population PK (PopPK) analysis may be used to assess the PK of milademetan and the relationship to response or biomarkers. The PK parameters for AZA will include Cmax, Tmax, and area under the plasma concentration-time curve up to time 6 hours (AUC6h). Induction of serum MIC-1 will be assessed as a PDy biomarker. Serum samples will be collected at multiple time points in the study to assess the effect of milademetan treatment on MIC-1 induction. Other exploratory PDy biomarkers may include, but are not limited to, expression levels of p53 and its target genes and DNA analysis to determine gene mutations, copy number variations, and CpG methylation status. Additional biomarkers both inside and/or outside of the p53 pathway may be included in order to better understand the responsiveness to therapy. **Efficacy Endpoints** The clinical activity of the treatment will be assessed using the 2017 European Leukemia Net recommendations for AML and the 2006 IWG response criteria for MDS. For subjects with AML, the efficacy endpoints will be CR, CRi, MLFS, PR, and stable disease (SD). Complete remission with partial hematological recovery (CRh) will be evaluated separately. For subjects with MDS, the efficacy endpoints will be CR, mCR, PR, cytogenetic response (complete or partial), SD, and hematologic improvement.
Statistical Analyses:	The primary analysis will occur after all subjects have either discontinued the study or completed at least 6 months of treatment. After the primary analysis, the main study will be closed. 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. Descriptive statistics will be provided for selected demographic, safety, PK, and PDy data by dose cohort at each timepoint as

appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented.

Safety Analyses

Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics. The Safety Analysis Set will include all enrolled subjects who received at least 1 dose of milademetan or AZA.

Pharmacokinetic Analyses

Plasma concentration data for milademetan and/or AZA will be summarized using descriptive statistics by dose cohort at each timepoint. The PK Analysis Set will include all subjects in the Safety Analysis Set who had measurable plasma concentrations of milademetan and/or AZA.

A PopPK analysis and exposure-response analyses for various endpoints may be developed. If developed, then the PopPK plan and the Technical Report will be provided separately.

Pharmacodynamic Analyses

Changes in MIC-1 levels in serum and other PDy parameters, if available, will be listed and summarized for the Safety Analysis Set using descriptive statistics by dose level cohort.

Efficacy Analyses

The efficacy endpoints will be listed and summarized using descriptive statistics based on the Full Analysis Set by dose for the combined Dose Escalation and Dose Expansion parts. For response rate, 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.

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ABBREVIATION	DEFINITION
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myelogenous leukemia
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC6h	Area under the plasma concentration-time curve up to time 6 hours
AUC24h	Area under the plasma concentration-time curve up to time 24 hours
AUCinf	Area under the plasma concentration-time curve up to infinity
AZA	5-Azacitidine
BCRP	Breast cancer resistance protein
BLRM	Bayesian logistic regression model
BUN	Blood urea nitrogen
CDKN2A	Cyclin-dependent kinase inhibitor 2A
CFR	Code of Federal Regulations
Cmax	Maximum plasma concentration
CNS	Central nervous system
CR	Complete remission
CRc	Composite complete remission
CRh	Complete remission with partial hematological recovery
CRi	Complete remission with incomplete blood count recovery
CRO	Contract research organization
CSPV	Clinical Safety and Pharmacovigilance
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Trough plasma concentration
CYP	Cytochrome P450
DDI	Drug-drug interaction
DLT	Dose-limiting toxicity(ies)
DNA	Deoxyribonucleic acid
DoR	Duration of composite complete remission

ABBREVIATION	DEFINITION
DS-3032a	The free form of DS-3032b
DSI	Daiichi Sankyo, Inc.
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EIU	Exposure In Utero
ELN	European LeukemiaNet
EWOC	Escalation with overdose control
GCP	Good Clinical Practice
GVHD	Graft-versus-host disease
HCT	Hematopoietic cell transplantation
hERG	Human ether-a-go-go related gene
HI	Hematologic improvement
HNSTD	Highest nonseverely toxic dose
IB	Investigator's Brochure
IC50	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonisation
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous(ly)
IWG	International Working Group
mCR	Marrow complete remission
MDM2	Murine double minute 2
MDM4	Murine double minute 4
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MIC-1	Macrophage inhibitory cytokine-1
MLFS	Morphologic leukemia-free state
MOLM-13	Leukemia cell line
MTD	Maximum tolerated dose

ABBREVIATION	DEFINITION
NCI	National Cancer Institute
OS	Overall survival
PD	Progressive disease
PDy	Pharmacodynamic(s)
P-gp	P-glycoprotein
PGx	Pharmacogenomics
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetics
PR	Partial remission
qd	Once daily
qd 3/14 × 2	Once daily for 3 of 14 days repeated twice in a 28-day cycle
qd 7/28	Once daily on Days 1 to 7 of a 28-day cycle
qd 14/28	Once daily on Days 1 to 14 of a 28-day cycle
qd 21/28	Once daily on Days 1 to 21 of a 28-day cycle
qd 28/28	Once daily on Days 1 to 28 of a 28-day cycle
QTcF	Corrected QT interval using Fridericia's formula
RBC	Red blood cell
RDE	Recommended dose for an expansion cohort
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAVER	Serious Adverse Event Report
SD	Stable disease
SID	Subject identification number
SJSA-1	Osteosarcoma cell line
SOC	System Organ Class
SOP	Standard operating procedure
SQ	Subcutaneous(ly)
SUSAR	Suspected unexpected serious adverse event reaction
TEAE	Treatment-emergent adverse event
Tmax	Time to reach maximum plasma concentration

ABBREVIATION	DEFINITION
TP53	The gene encoding p53
ULN	Upper limit of normal
WBC	White blood cell

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Investigational Products

1.1.1. Milademetan

DS-3032b (International Nonproprietary Name [INN]: Milademetan)

Milademetan is an orally available and highly selective inhibitor of the murine double minute 2 (MDM2)-p53 interaction.

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 "milademetan" unless indicated otherwise.

1.1.2. 5-Azacitidine

5-Azacitidine (INN: Azacitidine)

5-Azacitidine (AZA) is a pyrimidine nucleoside analog of cytidine and is indicated for the treatment of patients with myelodysplastic syndrome (MDS).[1]

1.2. Intended Use Under Investigation

Milademetan will be evaluated in subjects with relapsed or refractory (R/R) acute myelogenous leukemia (AML) or high-risk myelodysplastic syndrome (MDS) as a single agent in Part 1 and in combination with AZA in Part 1A. In Part 2, milademetan in combination with AZA will be evaluated in subjects with R/R AML, newly diagnosed AML unfit for intensive chemotherapy, or high-risk MDS.

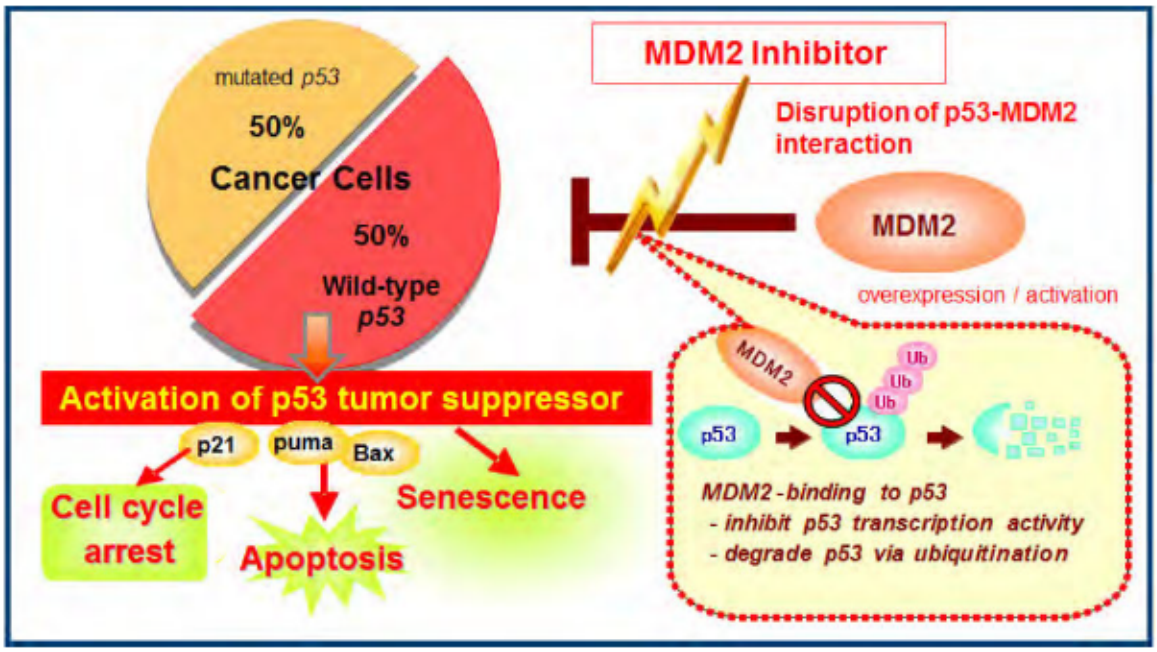
1.3. Pharmacological Target(s)

Milademetan, a novel, specific, small-molecule inhibitor of MDM2, disrupts interactions between MDM2 and the tumor suppressor protein p53 in tumor cells and is being developed as an oral drug for the treatment of cancer. The tumor suppressor protein p53 plays an essential role in preventing neoplasia by inducing cell cycle arrest or apoptosis in cells undergoing various types of physiological stress. However, inactivation of p53 by mutation occurs in a significant percentage of human tumors, resulting in a loss of tumor suppressor activity and thereby removing a pivotal barrier to neoplastic development.

Milademetan exerts antitumor activity by inhibiting interactions between MDM2 and p53 and preventing p53 degradation. The resulting increase in wild-type p53 activity activates transcriptional pathways important in inducing cell cycle arrest, apoptosis, and/or senescence in tumor cells.

The mechanism of action of milademetan is summarized in Figure 1.1.

Figure 1.1: Targeted Mechanism of Milademetan Antitumor Activity



Bax = Bcl-2-associated X protein; MDM2 = murine double minute 2; puma = p53 upregulated modulator of apoptosis; Ub = ubiquitin

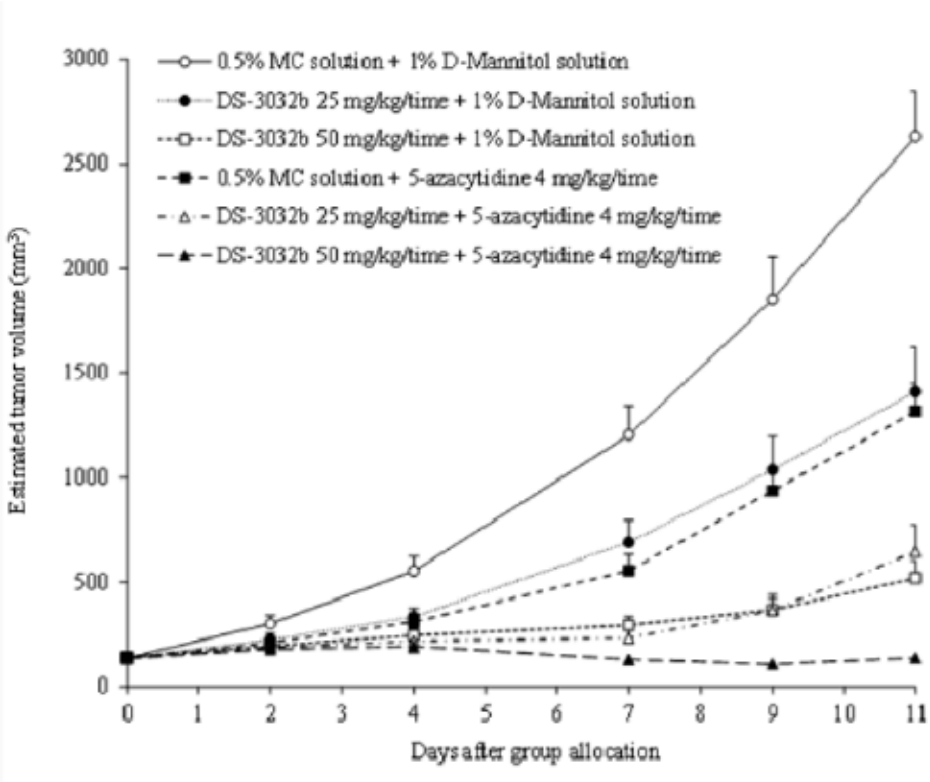
In human tumors that retain wild-type p53 protein, p53 activity is frequently inhibited by intermolecular interactions between p53 and MDM2. MDM2 and p53 form an autoregulatory feedback loop in which MDM2 maintains low levels of p53 activity in normal, unstressed cells, by promoting export of p53 out of the nucleus and proteasome-mediated degradation of p53 through its E3 ubiquitination ligase activity.[1] In the presence of stress, p53 becomes activated and subsequently acts as a transcription factor that modulates the expression of a variety of genes, including MDM2.[3] The MDM2 binding domain on p53 overlaps with the transcriptional activation domain of p53, thereby inhibiting the activity of p53. Thus, in human tumors, disruption of MDM2/p53 balance through overexpression and/or oncogenic activation of MDM2 allows tumorigenesis and tumor growth by preventing p53 function. Pharmacologic inhibition of the interaction between MDM2 and wild-type p53 in tumor cells could result in sustained increases in p53 activity and subsequent antitumor effects.[4,5] Therefore, pharmacologic restoration of the p53 pathway could be an effective strategy for cancer therapy targeting the wide array of human cancers that retain wild-type p53.[6]

1.4. Data Summary

Nonclinical pharmacology studies were conducted to demonstrate the role of milademetan in suppression of tumor growth. In vitro studies evaluated the potency of milademetan for inhibition of the MDM2-p53 interaction, the induction of p53-induced gene expression, and the inhibition of tumor growth in 6 human cancer cell lines. In addition, in vivo studies were conducted in a mouse model to demonstrate antitumor activity of milademetan after oral administration.

The effects of milademetan on human AML as single agent and in combination with a hypomethylating agent, AZA, were evaluated by treating the xenograft AML model (MOLM-13) with wild-type gene encoding p53 (TP53) in immunodeficient mice. Non-obese diabetic severe combined immunodeficient mice bearing MOLM-13 xenografts were treated with milademetan at 25 or 50 mg/kg/day for 11 days orally and with AZA at 4 mg/kg/day for 5 days, either as single agents or in combination. Antitumor effects were assessed based on estimated tumor volumes on Day 11. As can be seen in Figure 1.2, significant tumor growth inhibition compared to the untreated control were seen by treatment with the two dose levels of milademetan alone (46.4% and 80.3% for the 25 mg and 50 mg doses, respectively), and with AZA alone (49.6%). The combination treatment further increased the tumor growth inhibition (75.4% and 94.8%, respectively, for the 25 and 50 mg milademetan group in combination with 4 mg AZA). In this experiment, the mice were treated with milademetan and AZA concomitantly (starting from the same day) for 11 and 5 days, respectively.

Figure 1.2: Effects of Milademetan and 5-Azacitidine on Estimated Tumor Volume in MOLM-13-Bearing Non-Obese Diabetic Severe Combined Immunodeficient Mice



MC = methylcellulose
Note: Data points represent the mean for 10 animals. The vertical bars represent standard error.
Source: Milademetan Investigator's Brochure[7]

Safety pharmacology studies were conducted in compliance with Good Laboratory Practice regulations and evaluated the effect of milademetan on the cardiovascular system, central nervous system (CNS), and pulmonary system.

In vitro and in vivo data from these studies suggest a low risk potential on cardiovascular function in humans at milademetan exposures expected to be associated with clinical efficacy.

Effects on the CNS and pulmonary system were evaluated as part of a 4-week repeated dose toxicity study, in which no adverse effects on motor activity and no findings of physiological concern for effects on the pulmonary systems were noted.

Milademetan is a substrate for CYP3A and P-gp. A Phase 1 study in healthy subjects was conducted to evaluate the effect of co-administration of strong CYP3A4 inhibitors (itraconazole and posaconazole) on milademetan PK (Study DS3032-A-U107). Co-administration of milademetan 100 mg with itraconazole 200 mg, an antifungal and a strong CYP3A inhibitor, at steady state increased milademetan geometric 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 mean AUCinf by approximately 149%. Therefore, it is recommended that the dose of milademetan be reduced to 50% when it is concomitantly administered with a strong CYP3A4 inhibitors.

The direct inhibitory potential of milademetan on human CYP isoenzymes was studied in vitro and milademetan showed direct inhibition on CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5, but not on CYP1A2, and CYP2E1 (IC50 range: 7.8 μM to 27.0 μM). Milademetan also showed mild-to-moderate, metabolism-dependent inhibition of CYP3A4/5 (both testosterone 6β-hydroxylase and midazolam 1'-hydroxylase), but not on the other CYP isoenzymes examined. However, these levels (IC50 values) of milademetan are much higher than plasma concentrations at expected therapeutic doses in subjects and concomitant use of CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 substrates will therefore be permitted.

Additional information for ongoing studies and the most current safety and nonclinical information for milademetan can be found in the Investigator's Brochure (IB).[7]

1.4.1. Clinical Experience

A Phase 1 multiple ascending dose study (DS3032-A-U101) of milademetan in subjects with advanced solid tumors or lymphomas is currently ongoing. Another Phase 1 study of milademetan (DS3032-A-J103) in subjects with advanced solid tumors or lymphomas is also currently ongoing. In addition, another Phase 1 study of milademetan in combination with quizartinib (DS3032-A-U105) in subjects with FLT3-ITD mutant AML and a Phase 1 study of milademetan in subjects with AML in Japan (DS3032-A-J104) are ongoing.

Additional information on ongoing and completed studies can be found in the IB.[7]

1.5. Study Rationale

The tumor suppressor p53 is a transcription factor that plays a central role in preventing tumor development and progression by inducing cell cycle arrest, apoptosis, or senescence. TP53 suffers disabling somatic mutations or deletions in about 50% of all malignant tumors; p53 mutations are less frequent in leukemia, but are more common in an aberrant karyotype.[8] In tumors expressing wild-type protein, the tumor suppressor function of p53 may be attenuated by other mechanisms, such as over-expression of MDM2, a negative regulator of p53. MDM2

binds p53 with high affinity and negatively modulates the transcriptional activity and stability of the tumor suppressor. In leukemia with functional p53, inhibition of the MDM2-p53 interaction can restore p53 activity and is expected to offer a novel strategy for therapy.

AZA is a cytidine analogue that exerts its anti-leukemic activity by 2 mechanisms: direct cytotoxicity by incorporation into ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) (after conversion into the deoxyribonucleotide), and by inhibiting DNA methyl transferase 1 resulting in DNA hypomethylation, thus reversing the DNA hypermethylation of CpG islands reported in MDS, AML, and other malignancies.[9]

Since AZA is most toxic during S phase through incorporation into DNA and milademetan causes cell cycle arrest during G1 phase, mechanistically, the maximal effect of the combination is expected when the treatment is administered sequentially, with AZA first followed by milademetan.

This Phase 1, multiple ascending dose study will be conducted to assess the safety and tolerability of milademetan as a single agent and in combination with AZA, as well as to determine the PK/pharmacodynamic (PDy) response profile and preliminary efficacy of the drug in subjects with AML and MDS.

1.6. Risks and Benefits for Study Subjects

The safety, tolerability, and PK of AZA have been evaluated in humans. The most common reactions for AZA by subcutaneous (SQ) route are nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, injection site erythema, constipation, neutropenia, and ecchymosis. The most common adverse reactions by intravenous (IV) route also included petechiae, rigors, weakness, and hypokalemia.

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), myelosuppression (primarily thrombocytopenia), electrolyte disturbances, and DDIs with strong CYP3A inhibitors.

As of 02 May 2019, a total of 60 subjects with AML or high-risk MDS have received treatment as single agent under this protocol (DS3032-A-U102). The subjects were treated in a qd 21/28 dosing schedule at doses starting from 60 mg and at increasing doses of 90, 120, 160, and 210 mg. The MTD was determined to be 160 mg in the qd 21/28 dosing schedule in these subjects. A total of 57 of the 60 subjects have discontinued the study. Based on the increased tolerance and clinical benefit of the less frequent dosing schedule observed in the DS3032-A-U101 study in solid tumors, 15 subjects were treated under alternative dosing schedules as of 08 Jan 2018: 7 subjects at 160 mg qd 7/28, 3 subjects at 160 mg qd 3/14 × 2, 4 subjects at 160 mg qd for 14 of each 28-day cycle (qd 14/28), and 1 subject at 220 mg qd 14/28. Eight of the 60 subjects have experienced DLTs:

<u>qd 21/28 dosing schedule:</u>

- 1 subject at 60 mg (vomiting)
- 2 subjects at 160 mg (hypokalemia and diarrhea; 1 subject each)

- 3 subjects at 210 mg milademetan (nausea, fatigue, cellulitis, and renal failure; 1 subject each)

qd 14/28 dosing schedule:

- 2 subjects at 220 mg (nausea)

All 60 (100%) subjects who received treatment in the DS3032-A-U102 study experienced at least 1 TEAE. Overall, the most common TEAEs of any grade regardless of causality were nausea (42 [70%] subjects); diarrhea (33 [55%] subjects); vomiting (24 [40%] subjects); fatigue (21 [35%] subjects); decreased appetite, edema peripheral, and thrombocytopenia (14 [23.3%] subjects each); anemia (13 [21.7%] subjects); hypokalemia (12 [20.0%] subjects); hypotension, lung infection, and pneumonia (11 [18.3%] subjects each); hypomagnesemia, neutropenia, dyspnea, and sepsis (9 [15.0%] subjects each); and abdominal pain, asthenia, and dizziness (7 [11.7%] subjects each).

1.6.1. Potential Risk of Drug-Drug Interaction

Milademetan is a substrate for CYP3A and P-gp. A study in healthy subjects was conducted to evaluate the effect of co-administration of the strong CYP3A4 inhibitors (itraconazole and posaconazole) on milademetan PK (Study DS3032-A-U107). Co-administration of milademetan 100 mg with itraconazole 200 mg at steady state increased milademetan geometric mean Cmax and (AUCinf) by 8% and 115%. Similarly, posaconazole 200 mg at steady state increased milademetan geometric mean Cmax by approximately 19% and AUCinf by approximately 149%. Therefore, it is recommended that the dose of milademetan be reduced to 50% when it is concomitantly administered with a strong CYP3A4 inhibitors.

No formal clinical drug interaction studies with AZA have been conducted.

In vitro studies show that AZA is not an inhibitor or inducer of the CYPs tested (CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP1A2, CYP2E1, and CYP3A4); therefore, clinically relevant PK DDI are unlikely to occur between AZA and co-administered substrates of these CYP isozymes.[1] There appears to be limited potential for a DDI between milademetan and AZA. However, toxicokinetics in mice xenograft models suggest lower PK for milademetan when co-administered with AZA, and the PK of milademetan will be assessed. In addition, a substudy (n = 6) to exclude a potential effect of milademetan on AZA PK due to transporter inhibition (ie, P-glycoprotein [P-gp] and breast cancer resistance protein [BCRP]) will be conducted.

1.6.2. Potential Benefit Associated with Milademetan as a Single Agent and in Combination with 5-Azacitidine

Nonclinical data demonstrated that milademetan inhibited cell growth in a concentration-dependent manner and induced apoptosis, and was more potent than the well-characterized MDM2 inhibitor Nutlin-3a. In vivo studies demonstrated that multiple doses of milademetan produced statistically significant dose-related antitumor responses, with the highest dose of milademetan yielding a 93% tumor reduction relative to the control group. These data demonstrate that in tumors with wild-type p53, inhibition of MDM2-p53 interaction can restore p53 activity and is expected to offer a novel strategy for cancer therapy. Nonclinical in vivo

experiments using milademetan in combination with AZA demonstrated enhanced benefit of the combination treatment compared to the single-agent activities.

It is expected that the combination treatment of milademetan with AZA may increase the anti-leukemic activity by targeting 2 different malignant pathways based on the mechanism of action of these drugs, namely cytotoxic and hypomethylating effect of AZA and increased p53 activity by milademetan.

2. STUDY OBJECTIVES AND HYPOTHESES

2.1. Study Objectives

2.1.1. Primary Objectives

Part 1 and Part 1A

- To assess the safety and tolerability of milademetan as a single agent (Part 1) and in combination with AZA (Part 1A).
- To determine the MTD of milademetan as single agent and in combination with AZA and to identify a recommended dose for an expansion cohort (RDE) of milademetan plus AZA.

Part 2

- To confirm the safety and tolerability of milademetan in combination with AZA at the RDE and identify the recommended Phase 2 dose (RP2D).
- To evaluate the efficacy of milademetan in combination with AZA in subjects with AML or high-risk MDS.

2.1.2. Secondary Objectives

Part 1 and Part 1A

- To evaluate the PK of milademetan following single and multiple dosing.

Part 2

- To evaluate the PK of milademetan at the RDE.

2.1.3. Exploratory Objectives

Part 1 and Part 1A

- To evaluate efficacy of milademetan as a single agent (Part 1) and in combination with AZA (Part 1A) in R/R AML and high-risk MDS.
- To evaluate the relationship between leukemia response to milademetan as a single agent and in combination with AZA and the predictive biomarkers studied in pre-treatment bone marrow biopsies/aspirates and/or blood samples.
- To evaluate in serum the PDy effect of milademetan as a single agent and in combination with AZA on macrophage inhibitory cytokine-1 (MIC-1) levels.
- To assess other PDy effects of milademetan as a single agent and in combination with AZA on expression levels of p53 downstream genes, apoptosis markers, and/or other biomarkers in pre- and post-treatment bone marrow samples, if available.
- To assess the potential DDI of milademetan on AZA PK in a substudy (n = 6).

Part 2

- To evaluate the relationship between response to milademetan in combination with AZA in R/R AML, newly diagnosed AML unfit for intensive chemotherapy, or high-risk MDS and biomarkers.
- To evaluate in serum the PDy effect of milademetan in combination with AZA on macrophage inhibitory cytokine-1 (MIC-1) levels.
- To assess other PDy effects of milademetan in combination with AZA on expression of p53 downstream genes, apoptosis markers, and/or other biomarkers in pre- and post-treatment leukemic samples, if available.
- Additional assessments of efficacy.

2.2. Outcome Measures

2.2.1. Primary Outcome Measures

Part 1 and Part 1A

- Number of subjects with DLTs by the end of the Dose Escalation part (timeframe: within 5 years of first subject enrolled).

Part 1, Part 1A, and Part 2

- Number of subjects with treatment-emergent adverse events (TEAEs) (timeframe: within 6 years of first subject enrolled).

Part 2

- Number of subjects who achieved CR, CRi or MLFS for AML and who attained CR, marrow CR (mCR) or PR for high-risk MDS as the best response (timeframe: within 6 years of first subject enrolled).

2.2.2. Secondary Outcome Measures

Part 1, Part 1A, and Part 2

- Plasma concentrations and PK parameters of milademetan (timeframe: within 6 years of first subject enrolled).

2.2.3. Exploratory Outcome Measures

Part 1 and Part 1A

- Pharmacokinetic parameters of the combination of milademetan and AZA.

Part 1, Part 1A, and Part 2

- Pharmacodynamic and other biomarker measurements.
- Additional efficacy measurements.

2.3. Study Endpoints

2.3.1. Safety Endpoints

The 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 corrected QT interval using Fridericia's method (QTcF). Adverse events will be categorized using Medical Dictionary for Regulatory Activities (MedDRA) Version 17.0. Adverse events and laboratory test results will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (Version 4.03 before 01 Apr 2018).

2.3.2. Pharmacokinetic and Pharmacodynamic Endpoints

The PK parameters for milademetan will include Cmax, time to reach maximum plasma concentration (Tmax), trough plasma concentration (Ctrough), and area under the plasma concentration-time curve up to time 24 hours (AUC24h). Plasma samples for PK assessments will be taken at multiple time points in the study. In addition, population PK (PopPK) analysis may be used to assess the PK of milademetan and the relationship to response or biomarkers.

PK parameters for AZA will include Cmax, Tmax, and area under the plasma concentration-time curve up to time 6 hours (AUC6h) on Cycle 1/Day 1 (AZA alone) and Cycle 1/Day 7 (with milademetan starting on Day 5) for the first 6 subjects in Schedule e of Part 1A.

Induction of serum MIC-1 will be assessed as a PDy biomarker. Serum samples will be collected at multiple time points in the study to assess the effect of milademetan treatment on MIC-1 induction. Other exploratory PDy biomarkers including, but are not limited to, expression levels of p53, p21, MDM2, MDM4, apoptosis markers, and/or other biomarkers will also be assessed in bone marrow samples, if available.

2.3.3. Efficacy Endpoints

The efficacy endpoints will 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).

2.3.3.1. AML

The AML response in Part 1 and Part 1A will be assessed according to the 2003 International Working Group (IWG) response criteria (Section 17.4.4), while in Part 2, the 2017 European LeukemiaNet (ELN) recommendations will be applied (Section 17.4.1):

- CR rate
- CRi rate
- Composite complete remission (CRc) rate (CR+CRi)
- DOR (duration of composite complete remission): 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 (Part 2 only)
- Treatment failure (Part 1 and Part 1A only)
- CRh rate
    - CRh will be evaluated separately from the other response criteria

2.3.3.2. High-risk MDS

The response for high-risk MDS in all study parts will be assessed according to the 2006 IWG response criteria (Section 17.4.4):

- CR rate
- mCR rate
- PR rate
- Cytogenetic response (complete or partial) rates

Note: Study sites should report CR, mCR, PR, or cytogenetic response at each assessment by ignoring duration of response. However, CR, mCR, PR, or cytogenetic response which persists for at least 4 weeks will be summarized for the efficacy analysis.

Cytogenetic response (complete or partial) are not mutually exclusive to CR, mCR or PR rates. In other words, cytogenetic response (complete or partial) can be reported when CR, mCR or PR is reported.

- SD rate
- Hematologic improvement (HI) rate

Note: Study sites should report SD or HI at each assessment by ignoring duration of response. However, SD or HI which persists for at least 8 weeks will be summarized for the efficacy analysis.

2.3.3.3. Additional Efficacy Endpoints

Additional 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 or no intervening MDS therapy
- Event-free survival (EFS) for AML: Defined as time from first dose date until relapse after CR or CRi, refractory disease, or death from any cause, whichever is observed first

- Progression-free survival (PFS) for high-risk MDS: Defined as time from first dose date until relapse, disease progression, progression to AML, 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. Study Hypothesis

Milademetan as a single agent and in combination with AZA will be safe and well tolerated and will show clinical benefit in subjects with R/R AML, newly diagnosed AML unfit for intensive chemotherapy, or high-risk MDS. The study drugs will manifest activity as evidenced by response in subjects with R/R AML and newly diagnosed AML according to the 2003 IWG response criteria (Part 1 and Part 1A) and the 2017 ELN recommendations (Part 2), and in subjects with high-risk MDS according to the 2006 IWG response criteria (all parts).

3. STUDY DESIGN

3.1. Overall Plan

3.1.1. Study Type

This will be a Phase 1, open-label study of milademetan as a single agent (Part 1) and in combination with AZA (Part 1A) to assess its safety and tolerability and identify the MTD and RDE (in Dose Escalation) in subjects with R/R AML or high-risk MDS and to confirm the safety and tolerability of RDE and identify a RP2D (in Dose Expansion [Part 2]) in subjects with R/R AML, newly diagnosed AML unfit for intensive chemotherapy, or high-risk MDS.

Approximately 12 US sites are planned for Part 1 and Part 1A (Dose Escalation). Approximately 12 US sites are planned for Part 2 (Dose Expansion).

This 2-part study will include both a dose escalation portion, to identify the MTD of milademetan as a single agent and in combination with AZA and the recommended dose and schedule of milademetan and AZA combination for dose expansion cohorts (RDE), followed by a dose expansion portion, to confirm the safety and tolerability of milademetan and AZA combination, to determine the PDy in blood and/or bone marrow biopsies/aspirates, and to evaluate preliminary efficacy in subjects with R/R AML, newly diagnosed AML unfit for intensive chemotherapy, or high-risk MDS.

Milademetan as a single agent will be administered on a qd 21/28 schedule. An alternative drug administration schedule for dose escalation may be considered to evaluate the milademetan exposure relationship to PDy and toxicity. If the results indicate that using an alternative dosing schedule may provide less toxicity (eg, myelosuppression) while offering PDy benefits based on available biomarkers, dose escalation using this recommended alternative dosing schedule will be performed in lieu of, or in parallel with, the qd 21/28 schedule. The milademetan dose will also be evaluated in combination with AZA in Dose Escalation (Part 1A) followed by Dose Expansion (Part 2) (Table 3.1).

Table 3.1: Study Design

Part	Regimen	Cohort	Target Disease	Target Population	Estimated Enrollment (n)
Part 1 *Dose Escalation*	Milademetan single agent	Multiple escalating dosage/schedule cohorts	Relapsed/Refractory AML or high-risk MDS[a]	Subjects ≥18 years old	Approximately 24 to 36
Part 1A *Dose Escalation*	Milademetan and AZA	Multiple escalating dosage/schedule cohorts	Relapsed/Refractory AML or high-risk MDS[a]	Subjects ≥18 years old	Approximately 24 to 36
Part 2 *Dose Expansion*	Milademetan and AZA	Cohort 1	Relapsed/Refractory AML[b]	Subjects ≥18 years old	Approximately 41
		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 39
		Cohort 3	High-risk MDS	• Subjects ≥18 years old • Subjects who have not been treated for MDS or subjects who were previously treated with 1 or 2 treatment regimens for MDS	Approximately 39

AML = acute myeloid leukemia; AZA = 5-azacitidine; MDS = myelodysplastic syndrome
[a] There is no minimum or maximum number of prior AML or MDS treatment regimens for Part 1 and 1A.
[b] Part 2 includes more stringent criteria in terms of number of prior AML or MDS treatment regimens (Section 4.1.1).

3.1.2. Dose Escalation

Dose escalation of milademetan to determine the MTD will be guided by a Bayesian logistic regression model (BLRM) governed by the escalation with overdose control (EWOC) principle, with a starting dose of 60 mg based on safety and tolerability data obtained in the solid tumor or lymphoma first-in-human study of milademetan (Study DS3032-A-U101).

The dose increments for milademetan guided by BLRM with EWOC will also adhere to the following restrictions:

- The dose level increment should be no less than 30% in order to have distinction among dose levels considering the inter-subject variability in exposure, but flexibility may be applied in selecting the dose to accommodate the available dosage form strengths.
- The dose level increment should be no more than 100% even if the model suggests a higher dose than 100% for the next cohort.
- In the event of a DLT, the next 2 subjects in the current cohort will receive milademetan treatment starting at least 1 week apart.

The dose to be tested in the next cohort of subjects chosen by the Sponsor's clinical team and the Investigator(s) involved in the clinical study will be based on the dose by the BLRM, clinical assessment of toxicity profiles, and PK/PDy information available thus far.

Cohorts of 3 to 6 subjects will be enrolled and assessed for DLTs before escalation to a new higher dose. If 2 evaluable subjects in a cohort experience a DLT before the enrollment of the next subject, the model will be re-evaluated before enrollment of any additional subjects to the cohort. Enrollment of subjects to a new cohort requires completion of DLT evaluation of at least 3 subjects treated in the current cohort. Subjects who have neither completed a DLT evaluation nor experienced a DLT will be censored and not included in the BLRM update. In the event that subjects in the previous cohort experience a DLT after the enrollment of subjects to a new cohort has begun, 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 doses.

For a subject to be considered evaluable for dose escalation decisions, the subject must have received at least 75% of the doses during Cycle 1 or experienced a DLT in Cycle 1. The final MTD will be decided based on considerations of the respective MTD estimated by the BLRM and on an overall assessment of safety data from subsequent cycles and PK/PDy information collected at all doses tested.

Additional subjects for the characterization of safety, PK, or PDy may be added to 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.

3.1.2.1. Part 1 (Dose Escalation of Milademetan as a Single Agent)

3.1.2.1.1. Milademetan Starting Dose and Dose Schedule

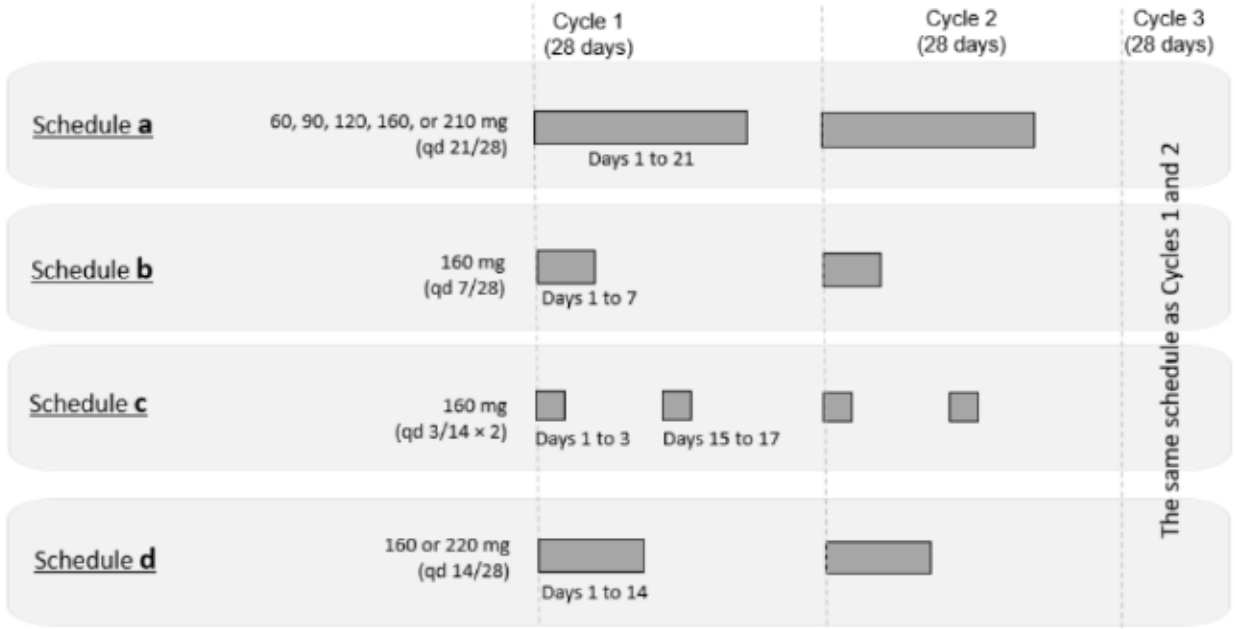
In an ongoing Phase 1 dose escalation study (Study DS3032-A-U101), milademetan was given as a single agent on a schedule of qd 21/28 to subjects with advanced solid tumors or lymphomas. The MTD in this schedule was determined to be 120 mg.

Based on the data from the DS3032-A-U101 study, the DS3032-A-U102 study in subjects with AML or high-risk MDS was started at a milademetan dose of 60 mg in the qd 21/28 schedule and the dose was escalated through 90 mg, 120 mg, 160 mg, and 210 mg.

The MTD in the qd 21/28 schedule has been determined to be 160 mg.

Figure 3.1 and Table 3.2 summarize the dosing schedule findings for milademetan as a single agent dose escalation in Part 1.

Figure 3.1: Dosing Schedule of Milademetan as a Single Agent (Part 1)



MTD = maximum tolerated dose; qd = once daily
Note: Information used to derive this figure was collected after finalization of protocol Version 3.0 on 10 May 2018.

Table 3.2: Dosing Schedule of Milademetan as a Single Agent (Part 1)

Cohort	Dosing Schedule	Schedule Description	Milademetan Dose Level	Note
Cohort 1	a	qd 21/28	60 mg	
Cohort 2	a	qd 21/28	90 mg	
Cohort 3	a	qd 21/28	120 mg	
Cohort 4	a	qd 21/28	160 mg	160 mg was determined as the MTD for qd 21/28 schedule.
Cohort 5	a	qd 21/28	210 mg	
Cohort 6	b	qd 7/28	160 mg	This dose/schedule was unable to control for leukemia proliferation.
Cohort 7	c	qd 3/14 × 2	160 mg	This dose/schedule was unable to control for leukemia proliferation.
Cohort 8	d	qd 14/28	160 mg	160 mg was determined as the MTD for qd 14/28 schedule.
Cohort 9	d	qd 14/28	220 mg	

MTD = maximum tolerated dose; qd = once daily
Note: Information used to derive this table was collected after finalization of protocol Version 3.0 on 10 May 2018.

3.1.2.1.2. Dose Escalation Using Alternative Milademetan as a Single Agent Schedule

Based on safety, PK, and PDy data collected during Dose Escalation using the qd 21/28 schedule of milademetan over 5 dose levels and reviewed by the Principal Investigators and Sponsor, alternative, less frequent dosing schedules were evaluated for dose escalation. Starting from the MTD dose level (160 mg) established for the qd 21/28 schedule, dose escalation using the following recommended alternative dosing schedules were performed in lieu of the qd 21/28 schedule allowing parallel evaluation:

- qd 7/28 schedule (Schedule b)
- qd 3/14 × 2 schedule (Schedule c)
- qd 14/28 schedule (Schedule d)

Dose escalation/de-escalation will follow the BLRM method as described above.

Note: After the finalization of Version 3.0 of this protocol on 10 May 2018, Study DS3032-A-U102 completed enrollment in Part 1, which evaluated milademetan as a single agent therapy in 4 different dose schedules (Schedules a to d). Although no DLTs were observed in the single cohorts of 160 mg schedules b (qd 7/28) and c (qd 3/14 × 2), respectively, neither schedule was able to control leukemia and neither was pursued further. In Schedule d (qd 14/28), when the dose was escalated from 160 mg with no DLTs in 3 subjects to the next higher dose of 220 mg, DLTs based on Grade 3 nausea were observed in the first 2 subjects. The dose was therefore de-escalated to 160 mg. However, no further enrollment was pursued at 160 mg in this dose schedule since the dose was same as the MTD determined in the more frequent dose schedule (Schedule a; qd 21/28).

3.1.2.2. Part 1A (Dose Escalation of Milademetan in Combination with AZA)

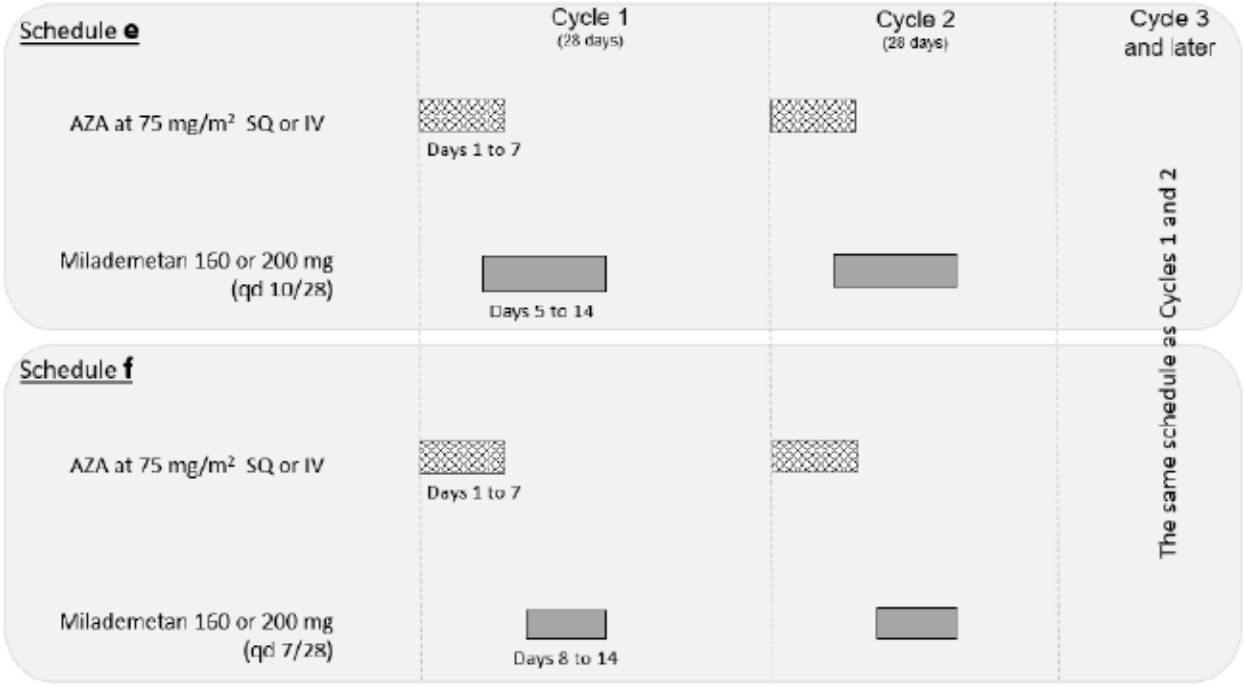
In Part 1A, subjects will be treated with AZA at 75 mg/m^2 SQ or IV in combination with escalating doses of milademetan. Two dosing schedules for milademetan will be evaluated (Figure 3.2 and Table 3.3). The starting dose for milademetan in combination with AZA will be 160 mg based on the MTD of milademetan as a single agent in the qd 21/28 schedule and will follow dose escalation per the BLRM with the EWOC principle.

In Schedule e, AZA will be administered on Days 1 to 7 and milademetan will be administered qd on Days 5 to 14 (with an overlap of both drugs administered on Days 5 to 7) in each 28-day cycle.

In Schedule f, AZA will be administered on Days 1 to 7 and milademetan will be administered qd on Days 8 to 14 in each 28-day cycle.

Both of the dosing schedules of milademetan may be evaluated in parallel.

Figure 3.2: Dosing Schedule of Milademetan in Combination with 5-Azacitidine



AZA = 5-azacitidine; IV = intravenous; qd = once daily; SQ = subcutaneous
Note: An alternative AZA schedule (Figure 3.3) will be tested in combination with milademetan at RDE (dose and dose schedule of RDE).

Table 3.3: Dosing Schedule of Milademetan in Combination with 5-Azacitidine

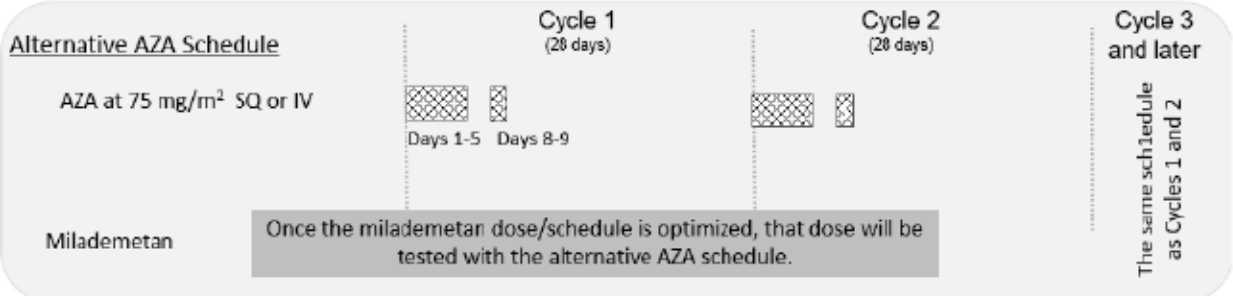
Cohort	Dosing Schedule	AZA (75 mg/m²)	Milademetan Dose Level	Milademetan Schedule
Cohort 10	e	Days 1 to 7	160 mg	qd 10/28 (Days 5 to 14)
Cohort 11	f	Days 1 to 7	160 mg	qd 7/28 (Days 8 to 14)
Cohort 12	e	Days 1 to 7	200 mg	qd 10/28 (Days 5 to 14)
Cohort 13	f	Days 1 to 7	200 mg	qd 7/28 (Days 8 to 14)

AZA = 5-azacitidine; qd = once daily

After the RDE (ie, the optimal dose and schedule of milademetan) is identified, an alternative schedule of AZA will be tested in combination with milademetan at RDE (only at the RDE dose and dose schedule). Instead of the 7-day consecutive administration from Days 1 to 7, AZA will be administered on Days 1 to 5 and then from Days 8 to 9 ("5+2"), with AZA dosing interruption during the weekend (eg, for logistic challenges such as closure of study sites or investigational pharmacy during the weekend) (Figure 3.3).

Both of the dosing schedules of milademetan (schedules e and f) may be evaluated in parallel during dose escalation.

Figure 3.3: Alternative 5-Azacitidine Dosing Schedule in Combination with Milademetan at RDE



AZA = 5-azacitidine; IV = intravenous; qd = once daily; SQ = subcutaneous

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

If a subject experiences prolonged thrombocytopenia (platelets $<50 \times 10^9$/L) and/or neutropenia (ANC $<0.5 \times 10^9$/L) that is drug-related in the Investigator's clinical judgement before 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 to 7/28 days, 7/28 days to 5/28 days, etc) in subsequent cycles while maintaining the same daily dose of milademetan.

3.1.3. Part 2 (Dose Expansion of Milademetan in Combination with AZA)

Upon completion of Part 1 and Part 1A with an established RDE and drug administration schedule, the Dose Expansion part will begin to confirm the safety and tolerability of milademetan in combination with AZA, to determine the PDy in blood and/or bone marrow biopsies/aspirates, and to evaluate preliminary efficacy and identify the RP2D. If the safety and efficacy data from the "1 to 7" and "5+2" schedules of AZA are comparable in the Dose Escalation, both AZA schedules will be allowed in Dose Expansion.

Three cohorts of approximately 40 subjects per cohort with AML or high-risk MDS will be concurrently enrolled and treated in Dose Expansion (total of approximately 120 subjects) as follows (see Section 4.1.1):

- Cohort 1: Subjects with R/R AML.
- Cohort 2: Subjects with newly diagnosed AML and are unfit for intensive chemotherapy.
- Cohort 3: Subjects with high-risk MDS.

Note: For Cohorts 1 and 3 of Part 2 (Dose Expansion), more stringent eligibility criteria regarding prior AML or MDS therapies will be applied in order to create a more homogenous subject population (Section 4.1).

3.1.3.1. Intrasubject Dose Escalation

No intrasubject dose escalation will be permitted.

3.2. Duration of the Study

The study duration is expected to last approximately 6 years from the time the first subject is enrolled in Part 1 of the study.

3.2.1. Duration of Subject Participation

The screening period is up to 14 days. Each cycle of treatment will be 28 days. The number of treatment cycles is not fixed in this study. 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.

3.2.2. Stopping Rules

The study may be terminated at any time and for any reason at the Sponsor's discretion.

3.3. Stopping Rule for Maximum Tolerated Dose Determination

The final MTD will be decided based on considerations of the respective MTD estimated by the BLRM and on an overall assessment of safety data from subsequent cycles and PK/PDy information collected at all different doses tested. For dose determination, the following stopping rules will be implemented for the Dose Escalation part: (a) at least 6 evaluable subjects have been enrolled at the MTD level with at least 18 evaluable subjects in total enrolled in the Dose Escalation part, (b) at least 9 evaluable subjects have been enrolled at a dose level which is the model's recommendation for the next dose cohort and for which the posterior probability of targeted toxicity is at least 50%, or (c) dose level -1 is too toxic.

3.4. Dose-limiting Toxicities

A DLT is defined as any TEAE not attributable to disease or disease-related processes that occurs during the observation period (Cycle 1) in each dose-level cohort and is Grade 3 or higher according to NCI-CTCAE Version 5.0 (Version 4.03 before 01 Apr 2018), with the exceptions as defined below.

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

- Grade ≥3 AST/alanine aminotransferase (ALT) levels lasting >3 days.
- AST/ALT >5 × ULN if accompanied by ≥Grade 2 elevation in bilirubin.

The following events are classified as DLTs:

- Subjects who are unable to complete at least 75% of the prescribed dose of milademetan or AZA in Cycle 1 as a result of non-disease-related Grade ≥2 events will be considered to have a DLT.
- Persistent bone marrow aplasia in the absence of malignant cell infiltration, per institutional guidelines, and failure to recover a peripheral absolute neutrophil count (ANC) $\geq 0.5 \times 10^9$/L and platelets $\geq 20 \times 10^9$/L while withholding study drug, resulting in a >2-week delay in initiating Cycle 2.

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 therapeutic antiemetic agents for managing established nausea or vomiting.
- Grade 3 diarrhea that has resolved to Grade ≤2 within 48 hours after standard antidiarrheal therapies.
- Isolated laboratory findings not associated with signs or symptoms including Grade 3/4 alkaline phosphatase, uric acid, amylase, and lipase elevations, and Grade 3 hyponatremia lasting <72 hours developed from Grade 1 at baseline.
- Due to the nature of AML and MDS, significant abnormalities of hematological parameters are expected from the underlying disease or as part of anticancer therapy. Therefore, no hematological DLTs are defined for this protocol.
- Alopecia.
- Grade ≥3 electrolyte abnormalities that are corrected to ≤Grade 1 within 24 hours.

3.5. Maximum Tolerated Dose and Recommended Dose for Expansion

Once the stopping criteria are met, the MTD estimated by BLRM and EWOC is the dose 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 less than 25% probability for the DLT rate >33% [probability for excessive or unacceptable toxicity]) (Section 3.1.2). Since an alternative milademetan administration schedule may be explored in lieu of or in parallel with the original qd 21/28 schedule and also in the combination of milademetan plus AZA, separate MTDs may be identified for each regimen. The final MTD for each dosing schedule will be decided based on considerations of the respective MTDs estimated by the BLRM and on an overall assessment of safety data from subsequent cycles and PK/PDy information collected at all different doses tested.

3.6. Management of Subjects with Adverse Events

Treatment-related toxicities meeting the DLT definition (see Section 3.4) occurring during the study will result in interruption and/or discontinuation of therapy. For subjects deriving clinical benefit from treatment, an option to resume the therapy at 1 dose level below that at which the toxicity occurred may be considered after the toxicity returns to NCI-CTCAE Grade ≤1 or to baseline values. However, subjects requiring more than 28 days to recover from acute toxicities should be withdrawn from the treatment. If a subject experiences NCI-CTCAE Grade 3 or 4 toxicity or an SAE that is unequivocally attributable to the underlying malignancy, milademetan treatment may be postponed until the toxicity has resolved to NCI-CTCAE Grade ≤1, or returns to baseline values.

3.7. Dose Interruptions and Reductions of Study Drug (s)

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

No dose modification for AZA is required with the concomitant administration of a strong CYP3A inhibitor.

The milademetan dose will be reduced when the concomitant administration of a strong CYP3A inhibitor is required:

- Milademetan dose will be reduced to half of the prescribed dose (ie, 120 mg and 160 mg doses of milademetan will be reduced to 60 mg and 80 mg, respectively).
- Regularly scheduled doses of milademetan after discontinuation of strong CYP3A inhibitor should be resumed after a 3-day washout period following discontinuation.

3.7.2. 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 milademetan and/or AZA and which persists >48 hours without improvement to ≤Grade 2 (or without waiting 48 hours if in the Investigators judgment the AE poses a serious risk to the subject). This will not apply for Grade 3 fatigue lasting <48 hours.

- Dosing will be interrupted for up to 28 days.
    - If toxicity improves to ≤Grade 1 within 28 days, treatment may be resumed at the previous dose.
    - If toxicity improves to Grade 2 within 28 days, treatment may be resumed at a reduced dose (1 level below) for milademetan and/or AZA only after the toxicity has resolved to ≤Grade 1. Alternatively, for milademetan, the Investigator after consultation with the Sponsor Medical Monitor may reduce the dose frequency (eg, qd 10/28 days to qd 7/28 days, qd 7/28 days to qd 5/28 days, etc) in subsequent cycles while maintaining the same daily dose of milademetan.
    - For other Grade ≥2 laboratory abnormalities that do not meet the criteria for DLTs, treatment continuation with milademetan will be at the discretion of the Investigator.
- If toxicity does not improve/resolve within 28 days, then treatment may be discontinued after discussion between the Investigator and Sponsor Medical Monitor.

3.7.3. Dose Interruptions and Reductions for Hematologic Toxicities

Neutropenia and/or thrombocytopenia are anticipated hematologic toxicities for both milademetan and AZA. Either or both of the study drugs can be interrupted and/or dose reduced per the Investigator's clinical opinion of attributions to the disease or the study drug(s). The Investigator should consult the Sponsor Medical Monitor if attributions are not clear.

3.7.3.1. Milademetan

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

- Upon consultation with the Sponsor Medical Monitor, the Investigator may:
  - Reduce the milademetan dose frequency (eg, qd 10/28 days to qd 7/28 days, qd 7/28 days to qd 5/28 days, etc) while keeping the same dose level, OR
  - Reduce the dose of milademetan by 1 dose level while keeping the same dosing schedule.
- If toxicities persist, the Investigator should discuss with the Sponsor prior to any additional dose reductions of either AZA or milademetan.

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

3.7.3.2. 5-Azacitidine

For subjects without reduced baseline blood count (eg, WBC $\geq 3.0 \times 10^9$/L, ANC $\geq 1.5 \times 10^9$/L, and platelets $\geq 75.0 \times 10^9$/L) prior to the study drug treatment, the dose will be adjusted per Table 3.4, based on nadir counts for any given cycle.

Table 3.4: 5-Azacitidine Dosage Adjustments Based on Nadir Counts

Nadir Counts		% Dose in the Next Course
ANC ($\times 10^9$/L)	Platelets ($\times 10^9$/L)	
<0.5	<25.0	50%
0.5 – 1.5	25.0 – 50.0	67%
>1.5	>50.0	100%

ANC = absolute neutrophil count
Source = Vidaza® (azacitidine for injection) package insert[1]

For subjects with reduced baseline blood count (eg, WBC $<3.0 \times 10^9$/L, ANC $<1.5 \times 10^9$/L, and platelets $<75.0 \times 10^9$/L) prior to the study drug treatment, dose adjustments should be based on nadir counts and bone marrow biopsy cellularity at the time of the nadir as noted in Table 3.5, unless there is clear improvement in differentiation (percentage of mature granulocytes is higher and ANC is higher than at onset of that course) at the time of the next cycle, in which case the dose of the current treatment should be continued.

If a nadir as defined in Table 3.4 has occurred, the next course of treatment should be given 28 days after the start of the preceding course, provided that both the WBC and the platelet counts are >25% above the nadir and are rising. If a >25% increase above the nadir is not seen by Day 28, counts should be reassessed every 7 days. If a >25% increase is not seen by Day 42, then the patient should be treated with 50% of the scheduled dose.

Table 3.5: 5-Azacitidine Dosage Adjustments Based on Nadir Counts

WBC or Platelet Nadir % Decrease in Counts from Baseline	Bone Marrow Biopsy Cellularity at Time of Nadir		
	30% – 60%	15% – 30%	<15%
	% Dose in the Next Cycle		
50% – 75%	100%	50%	33%
>75%	75%	50%	33%

WBC = white blood cell
Source = Vidaza® (azacitidine for injection) package insert[1]

3.7.4. Dosage Modifications for 5-Azacitidine Based on Renal Function and Serum Electrolytes

If unexplained reductions in serum bicarbonate levels to <20 mEq/L occur, the dosage should be reduced by 50% on the next course. Similarly, if unexplained elevations of blood urea nitrogen (BUN) or serum creatinine occur, the next cycle should be delayed until values return to normal or baseline, and the dose should be reduced by 50% on the next treatment course.

4. STUDY POPULATION

Subjects with R/R AML or high-risk MDS will be enrolled in Part 1 (Dose Escalation) for milademetan as a single agent and in Part 1A (Dose Escalation) for milademetan in combination with AZA. Part 2 (Dose Expansion) will examine milademetan in combination with AZA in subjects with R/R AML, newly diagnosed AML unfit for intensive chemotherapy, or high-risk MDS. Specific inclusion and exclusion criteria are available in Section 4.1.1 and Section 4.1.2.

4.1. Enrollment

Investigators will maintain a confidential screening log of all potential study candidates that includes limited information of the subjects (initials, age, sex), and date and outcome of screening process (eg, enroll in the study, reason for ineligibility, refused to participate).

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 who have been allocated to study numbers upon enrolling in the study allows the Investigator to reveal the identity of any subject when necessary.

Each subject or legally acceptable representative will be provided with information about the study, will have all questions answered to their satisfaction, and will sign and date an informed consent form (ICF). This will be completed before any study-specific procedures are performed. Additional information about informed consent procedures is provided in Section 6.1.1.

A subject is considered enrolled in the study upon the Investigator or designee obtaining written informed consent from the subject or the subject's legally acceptable representative (Section 6.1.1) and upon determination that all inclusion and exclusion criteria have been satisfied. After assigning a subject identification number (SID) to each subject at the time of Screening, Investigators will assess the eligibility of a subject based on the inclusion and exclusion criteria after obtaining written informed consent from the subject. After assessment by Investigators, the inclusion criteria/exclusion criteria form will be completed for registration. The Sponsor will perform registration after verifying that the subject meets the inclusion/exclusion criteria provided by the Investigator. Directly after registration, the Sponsor will forward the results of registration to the Investigator. At that time, the subject will be assigned to study drug treatment.

Data for all study visits will be recorded on the eCRF for subjects who receive study drug treatment. Only minimal data (ie, demography and reason for withdrawal) will be recorded on the eCRF for subjects who fail inclusion/exclusion criteria and/or do not receive study drug. Further data, such as AEs, will not be collected from subjects once they are considered screen failures or have decided to withdraw prior to receiving study drug.

4.1.1. Inclusion Criteria (Part 1/1A and Part 2)

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, or high-risk MDS (defined by Revised International Prognostic Scoring System score of High or Very High [Section 17.6]).

   - Part 1 and 1A (Dose Escalation)
     - Subjects with R/R AML, OR

       Subjects with untreated, high-risk MDS or subjects who have received prior MDS treatment regimens.
     - Subjects ≥18 years old.

     Note: There is no minimum or maximum number of prior AML or MDS treatment regimens for Part 1 and 1A.

   - Part 2 (Dose Expansion)
     - Cohort 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
         - Subjects have received 1 to 3 prior treatment regimens for AML if prior treatments included an intensive chemotherapy (eg, anthracycline-based therapy and/or intermediate or high dose of cytarabine), OR

           Subjects who have received 1 to 2 prior treatment regimens for AML if prior treatments did not include an intensive chemotherapy.
       - Subjects ≥18 years old.
     - Cohort 2: newly diagnosed AML
       - Subjects with newly diagnosed AML who are ineligible for intensive induction chemotherapy (eg, combination of an anthracycline and cytarabine). Subjects must have had no prior AML treatment, with the exceptions of therapy for antecedent hematologic malignancies (eg, azacitidine for MDS) or hydroxyurea.
       - Subjects ≥75 years old, OR

         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, or 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.

  - Cohort 3: high-risk MDS
    - Subjects with untreated, high-risk MDS or who received up to 2 prior MDS treatment regimens. Prior MDS therapy here excludes supportive care such as transfusion, or erythropoiesis-stimulating agent.

2. Has an Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.
   - As an exception, subjects with newly diagnosed AML between 18 and 74 years old (inclusive) in Part 2 Cohort 2 with ECOG Performance Status of 3 will be eligible.
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 creatinine clearance 50-60 mL/min AND has serum creatinine ≤1.5 × ULN. In obese subjects, the lean body weight can be used in the equation instead of actual body weight.
4. Has adequate hepatic function, defined as:
   - AST/ALT ≤2.5 × ULN (≤5 × ULN if deemed elevated due to leukemia), and
   - Serum total bilirubin ≤1.5 × ULN (≤3 × ULN if deemed elevated due to leukemia or in subjects with documented Gilbert's Syndrome).
5. Subject (or legally acceptable representative) is able to provide written informed consent, comply with protocol visits and procedures, and take oral medication, and does not have any active infection or comorbidity that would interfere with therapy.
6. 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 (Section 17.9) 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).

   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.

7. Subject must be fully informed about their illness and the investigational nature of the study protocol (including foreseeable risks and possible side effects).
8. Subject must sign and date an Institutional Review Board (IRB)-approved ICF (including Health Insurance Portability and Accountability Act authorization, if applicable) before performance of any study-specific procedures or tests.
9. Able and willing to provide bone marrow biopsies/aspirates as requested by the protocol.
10. Is willing to undergo malignancy genotyping for TP53 mutation, insertion, or deletion at Screening.

4.1.2. Exclusion Criteria

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

1. Has a diagnosis of acute promyelocytic leukemia.
2. Has a malignancy that is known to contain a non-synonymous mutation, insertion, or deletion in the TP53 gene determined previously or at Screening.
3. Presence of 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.
4. Has other concurrent primary malignancy that required systemic anti-neoplastic treatment within the previous 2 years, except for localized cancers that have apparently been cured, such as non-melanoma skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast.
5. Any condition that would preclude adequate absorption of milademetan, including refractory nausea and vomiting, malabsorption, biliary shunt, significant bowel resection, and/or graft-versus-host disease (GVHD) affecting the gut.
6. Has an uncontrolled infection requiring IV antibiotics, antivirals, or antifungals.
7. Has known human immunodeficiency virus (HIV) infection with evidence of active infection by HIV RNA viral load, or active hepatitis B or C infection based on positive tests during Screening.
8. Has a concomitant medical condition that would increase the risk of toxicity.
9. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to NCI-CTCAE Grade ≤1, or baseline. Subjects with chronic Grade 2 toxicities may be eligible per discretion of the Investigator and Sponsor (eg, Grade 2 chemotherapy-induced neuropathy).
10. Has received hematopoietic cell transplantation (HCT) within 60 days of the first dose of study drugs.
11. Clinically significant 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.

12. Is receiving concomitant treatment with a strong inducer of CYP3A4/5 or consumption of St. John's Wort (hypericin) within 3 days prior to the first dose and during treatment.
13. Received anti-AML therapy (except for hydroxyurea) or anti-MDS therapy 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.
    - Hydroxyurea must be discontinued at least 48 hours prior to study treatment.
14. Had major surgery within 4 weeks prior to study drug treatment.
15. Participated in a therapeutic clinical study within a washout time of 2 weeks or 5 half-lives of the drug/biologic (whichever is longer) before starting study drug treatment under this protocol, or current participation in other therapeutic investigational procedures.
16. Uncontrolled or significant cardiovascular disease, including:
    a. Prolongation of QTcF at rest, where the mean QTcF interval is >480 ms based on triplicate ECGs.
    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. NYHA Class III or IV congestive heart failure (Section 17.8).
    i. Known LVEF ≤50% or institutional lower limit of normal.
        - As an exception, subjects with newly diagnosed AML between 18 and 74 years old in Part 2 Cohort 2 with LVEF ≤50% or institutional lower limit of normal will be eligible.
    j. Uncontrolled hypertension.
    k. Left bundle branch block.
17. Known DLCO ≤65% or FEV1 ≤65%.

- As an exception, subjects with newly diagnosed AML between 18 and 74 years old in Part 2 Cohort 2 with DLCO ≤65% or FEV1 ≤65% will be eligible.

18. Pregnant or breastfeeding.
19. Substance abuse or medical, psychological, or social conditions that, in the opinion of the Investigator, may interfere with the subject's participation in the clinical study or evaluation of the clinical study results.
20. Prior treatment with an MDM2 inhibitor.

4.2. Discontinuation

A subject may discontinue from study drug treatment, but may agree to receive long-term follow-up phone call and/or site visit to collect survival data.

4.2.1. Study Treatment Discontinuations

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

- AE
- Death
- Progressive disease (PD) or relapse which meets protocol-defined criteria (Section 17.4 and Section 17.5)
- Clinical PD or relapse based on Investigator's judgement
- Allogeneic HCT
- Pregnancy
- Protocol deviation
- Lost to follow-up
- Withdrawal by subject's decision
- 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 study drug treatment until the Investigator has alternative AML or MDS 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.

4.2.2. Study Discontinuation

Subjects may be withdrawn from the study at any time after signing the ICF for the following reasons:

- Withdrawal by subject's decision
- Death
- PD or relapse
- Lost to follow-up
- Other (the reason should be specified on the CRF)

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

All subjects who are withdrawn from the study should complete protocol-specified End-of-treatment (Section 6.5) and Follow-up procedures (Section 6.6).

4.2.3. Subject Replacement

During Parts 1 and 1A of the study, any subject who discontinues study participation before completing the first cycle of treatment and is not evaluable for DLT may be replaced. See Section 3.4 for definitions of DLTs.

4.2.4. Subject Re-screening Procedures

Re-screening is permitted for any subject who failed to meet eligibility criteria upon initial screening. The SID 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.

Bone marrow biopsy/aspirate is not required to be repeated if bone marrow specimen were already submitted during the previous screening and if the disease condition is not considered to have significantly changed since the initial screening sample based on the Investigator's clinical judgement. Additionally, the Investigator may opt to not repeat other screening tests after discussion with the Sponsor Medical Monitor.

5. TREATMENTS ADMINISTERED

5.1. Investigational Products

5.1.1. Randomization and Blinding

Not applicable.

5.1.2. Labeling and Packaging

Milademetan 5 mg, 20 mg, 80 mg, and/or 200 mg capsules will be supplied in individually packaged desiccant-embedded aluminum blister cards (wallets), each containing 7 capsules; milademetan 30 mg, 80 mg, and/or 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.

Azacitidine for injection is commercially available as a lyophilized powder in 100 mg single-dose vials, packaged in cartons of 1 vial.

The clinical site will dispense take-home milademetan with labels and instructions.

5.1.3. Preparation

Procedures for proper handling and disposal of anticancer drugs should be followed in accordance with the standard operating procedures (SOPs) of the study site.

5.1.4. Administration

Milademetan will be administered as a single oral capsule or as a combination of multiple oral capsules. For Part 1A and Part 2, milademetan will be administered in 2 schedules in combination with AZA: Schedule e on Days 5 to 14 and Schedule f on Days 8 to 14.

AZA will be reconstituted in sterile water for use according to the package insert for SQ or IV administration. Subjects will be treated with AZA at 75 mg/m^2 SQ or IV administered on Days 1 to 7 in combination with milademetan in the selected dosing schedule. After the RDE is identified, an alternative AZA schedule (administration on Days 1 to 5 followed by Days 8 to 9, Figure 3.3) will be evaluated to determine whether treatment of AZA in both the schedules can be allowed in the Dose Expansion cohorts.

Study drug administration that occurs at clinic visits will be supervised by a member of the site staff.

5.1.5. Storage

Drug supplies must be stored in a secure, limited access storage area under the recommended storage conditions listed below:

- Milademetan in blister cards: Stored at 2°C to 8°C (36°F to 46°F).
- Milademetan in HDPE bottles: Stored at room temperature up to 25°C.
- AZA: Stored according to label information.

If storage conditions are not maintained per specified requirements, the CRO or the Sponsor should be contacted.

5.1.6. 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, drug expiration date, and sign the Receipt of Shipment Form provided. The Receipt of Shipment Form should be faxed as instructed on the form. The original will be retained at the site. 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 drug. The record must be kept current and should contain the dates and quantities of drug received, subject (identification number 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, if from individual subject drug units, as well as the initials of the dispenser.

At the end of the study, or as directed, all milademetan capsules including unused, partially used, or empty containers will be returned to a designee as instructed by the Sponsor. Study drug will be returned 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 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/delegate and the Sponsor/delegate has received copies of the site's drug handling and disposition SOPs.

All study drug inventory forms must be made available for inspection by a Sponsor-authorized representative or designee and regulatory agency inspectors. The Investigator is responsible for the accountability of all used and unused study supplies at the site.

5.1.7. Retention Samples

Not applicable.

5.2. Method of Assessing Treatment Compliance

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

- Milademetan only to subjects participating in the study and complying with the instructions from the clinical study personnel.
- Doses on the visit days should be administered to subjects under the supervision of clinical study personnel at the site.
- Milademetan may be dispensed in amounts exceeding the minimum amount required for the period of time until the next visit. Subjects will be instructed to return all unused milademetan 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.

- AZA will be administered by SQ or IV route by the site staff during the site visit to ensure compliance.

5.3. Concomitant Medications

All anticancer medications that the subject received at any time point will be recorded from the medical history irrespective of the time relative to Screening. All non-cancer medications received by subjects within 30 days prior to Screening will also be recorded as prior medications. All concomitant medications will be recorded on the eCRF.

Concomitant use of hydroxyurea is permitted in Cycle 1 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, it should be discussed with Sponsor. However, hydroxyurea should preferably be avoided on Days -2 to 15 of Cycle 1 within which blood samples will be collected for characterization of PDy effects.

Subjects should avoid strong CYP3A4 inhibitors while entering the study. See Section 3.7.1 for dosing instructions if the concomitant administration of a strong CYP3A inhibitor is required.

5.3.1. Prohibited Concomitant Medications/Activities

The following medications and products will be prohibited:

- Other hematological malignancy therapy, including cytotoxic, antibody, or retinoid, and small-molecule tyrosine kinase inhibitors.
- Other investigational agents.
- Grapefruit juice, a CYP3A inhibitor, and foods or beverages containing grapefruit should be avoided throughout the duration of the study.
- Drugs that are inducers of CYP3A or St. John's wort (hypericin) will not be permitted for 3 days before and throughout the duration of the study.

6. STUDY PROCEDURES

Summary descriptions of the study procedures are presented below. Refer to the Schedule of Events tables provided in Section 17.1 for visit-by-visit listings of procedures.

6.1. Screening/Subject Eligibility Procedures

Generate a subject ID (SID) and review the subject's demographics, medical and target disease history (including DoR following the most recent therapy and prior medication history information for cancer), vital signs, and examinations (eg, physical exam, ECOG/MUGA, ECG, ECOG PS, laboratory assessments) and compare against the eligibility criteria.

A serum sample for pregnancy testing and a follicle stimulating hormone (FSH) test to confirm menarche are required for female subjects of childbearing potential.

6.1.1. Informed Consent

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or any study drugs are administered. Subjects should be given the opportunity to ask questions and receive responses to their inquiries and should have adequate time to decide whether or not to participate in the study. Refer to Section 15.1.2 for additional details.

6.1.2. General Medical History and Baseline Conditions

Subject's medical history will be obtained by the investigator or a qualified designee.

Untoward medical occurrence (including clinically relevant laboratory values that are not symptoms of AML or MDS, or vital signs that are out of range) that were diagnosed or known to exist prior to the first dose of study medications will be recorded on the General Medical History and Baseline Conditions eCRF, not on the AE eCRF. Record the start date of any medical occurrence that started after ICF was signed and is ongoing at the time of the first dose of study drug on the General Medical History and Baseline Conditions eCRF.

6.1.3. Left Ventricular Ejection Fraction

Measure LVEF by either echocardiogram (ECHO) or multigated acquisition (MUGA) scan. ECHO/MUGA do not need to be repeated if the procedure was done within 60 days before the first dose of study drugs and if no changes in cardiac conditions were observed based on the Investigator's clinical assessment.

6.1.4. Qualifying Bone Marrow Evaluation

A bone marrow evaluation is required at Screening for all subjects in the study. Bone marrow biopsies/aspirates or blood samples for centralized TP53 genotyping and/or other markers such as gene signature will be required at Screening for all subjects.

6.2. Efficacy Procedures

Bone marrow biopsies/aspirates and blood samples for disease assessment will be performed according to the Schedule of Events. See Section 7 for additional details.

6.3. Safety Procedures

6.3.1. Adverse Events and Concomitant Medications

Collect AEs and concomitant medications as indicated in the Schedule of Events. Refer to Section 9.3 for additional details on AEs.

6.3.2. Vital Signs

Vital signs will include the measurements of systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, height (obtained once, prior to dosing), and body weight. Blood pressure and pulse rate will be measured after the subject has rested supine for 5 minutes or more and prior to laboratory draws.

6.3.3. Clinical Laboratory Assessments

Clinical laboratory tests, including hematology and blood chemistry, will be performed and will be sent to the central laboratory for analysis. Refer to Section 9.6 for the complete list of laboratory parameters.

6.3.4. 12-lead Electrocardiogram

Triplicate 12 lead-electrocardiograms (ECGs) will be performed and recorded for every subject after the subject has rested in a supine position for 5 minutes or more. The 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes. Abnormal, clinically relevant findings occurring post-baseline will be reported as AEs.

6.3.5. Eastern Cooperative Oncology Group Performance Status

Assess and record the subject's ECOG performance status (Section 17.1).

6.4. Pharmacokinetic/Pharmacodynamic Procedures

6.4.1. Pharmacokinetic Blood Samples

Blood samples for PK assessments will be collected at the timepoints indicated in the Schedule of Events. Refer to Section 8.1 for details on the PK collection timepoints by study part and schedule.

6.4.2. Biomarker Analysis Using Blood or Bone Marrow Samples

Blood samples for biomarker analyses will be collected per the Schedule of Events; additionally, post-Screening, the samples should be collected at matching timepoints to bone marrow biopsies/aspirates if not otherwise noted on the Schedule of Events (eg, in cases of unscheduled bone marrow biopsies).

Some of the biomarker analysis, such as leukemic stem cell enrichment, TP53, and MIC-1 assays, will be done using blood or bone marrow biomarker samples that will be collected as indicated. Any leftover samples after these analyses will be used to explore RNA, DNA, or other protein assays. Upon completion of the biomarker analyses, these samples will be stored for 15 years for future exploratory analysis related to drug or disease, or for other biomarker assays. Subject consent will be obtained for long term storage and use of samples.

Refer to Section 8.2 for additional details on biomarker tests and analyses.

6.4.3. Blood Sample for Banking Plasma

Collect peripheral blood for banking plasma for future exploratory molecular analysis of biomarkers on Cycle 1/Days 1 and 14, Cycle 2/Day 1, Cycle 3/Day 1, and then every 3 cycles thereafter (ie, Cycles 6, 9, 12, etc) corresponding to the timepoints for bone marrow biopsy/aspirate. Cycle 1/Day 14 sample collection will be moved to Day 15 for subjects on the alternative (5+2) AZA schedule (Figure 3.3).

6.4.4. Buccal Swab for Pharmacogenomics

Obtain a buccal swab for PGx. Refer to Section 8.3 for additional details and to the Study Manual for instructions on handling and shipping of the PGx sample.

6.5. End-of-treatment - Part 1/Part 1A 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, but before beginning any other form of anticancer therapy.

Perform the assessments as listed in the Schedule of Events, including bone marrow re-biopsy/re-aspirate and time-matched blood for biomarkers.

6.5.1. End-of-treatment Bone Marrow Re-biopsy (Part 1/Part 1A and Part 2)

To search for possible mechanisms of acquired resistance to milademetan and AZA combination, a bone marrow re-biopsy or re-aspirate (and time-matched blood for biomarkers) will be performed in AML 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, and in high-risk MDS subjects who achieved an initial CR, mCR, or PR but later relapsed while on therapy while on therapy. Bone marrow re-biopsy or re-aspirate should be performed within 30 days following the last dose of study drugs, prior to initiating subsequent AML or MDS therapy.

6.6. Follow-up Phase

All subjects who complete/discontinue study treatment will enter the Follow-up phase and will undergo the following assessments.

6.6.1. 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 medication(s). Follow-up information will be collected via a phone call or site visit. If the subject begins another form of anticancer therapy before the end of the 30-day period, every effort should be made to complete all the End-of-study assessments prior to commencing the

new AML or MDS therapy. 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 or MDS therapy.
- HCT and HCT-relevant information, if performed.

6.6.2. 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 as feasible:

- Subject survival status.
- Date and cause of death, if applicable.
- Subsequent AML or MDS 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 as possible the specific reason for inability to collect long-term follow-up data.

6.7. Protocol Deviations

The Investigator should conduct the study in compliance with the protocol agreed to by the Sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB.

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. The Sponsor must be notified of all intended or unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

The Investigator, or person designated by the Investigator, should document and explain any deviation from the approved protocol.

If a subject was ineligible or received the incorrect dose of study drug, and had at least 1 administration of study drug, data should be collected for safety purposes.

The Investigator should notify the IRB of deviations from the protocol in accordance with local procedures.

7. EFFICACY ASSESSMENTS

7.1. Efficacy Variable(s)

Efficacy assessments will be based on Investigator 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). The AML response in Part 1 and Part 1A will be assessed according to the 2003 IWG response criteria (Section 17.4.4), while in Part 2, the 2017 ELN recommendations will be applied (Section 17.4.1). The response for high-risk MDS in all study parts will be assessed according to the 2006 IWG response criteria (Section 17.5.1).

The percentage of subjects undergoing allogeneic HCT directly following protocol-specified treatment with no intervening AML or MDS therapy and transfusion independency is based on Investigators' reports. The efficacy endpoints are listed in Section 2.3.3.

7.1.1. Bone Marrow Biopsies/Aspirates (Subjects with AML)

Figure 7.1 presents the schedule for bone marrow biopsies/aspirates in subjects with AML. During the first 12 cycles:

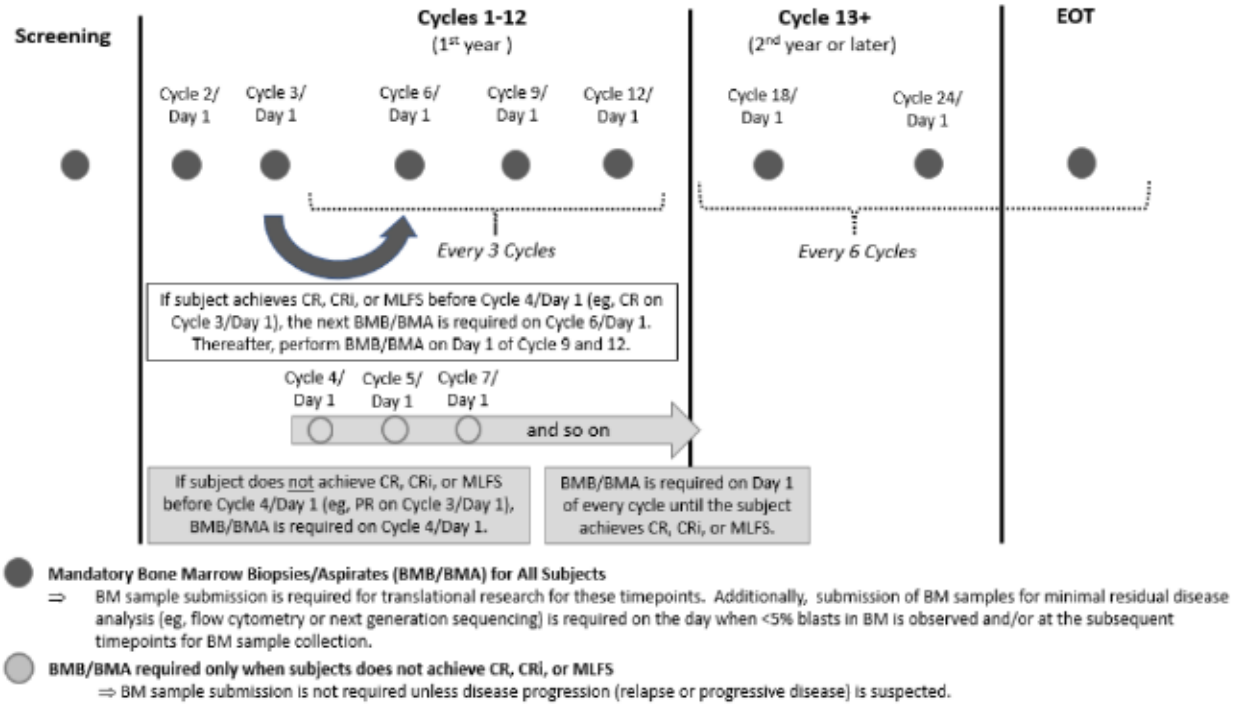
- Bone marrow biopsies/aspirates are mandated on Day 1 of Cycles 2 and 3 for all subjects.
    - If subject achieves CR, CRi, or MLFS before Cycle 4/Day 1 (eg, CR on Cycle 3/Day 1), bone marrow biopsies/aspirates will not be required on Cycle 4/Day 1.
        - Perform bone marrow biopsies/aspirates on Day 1 of Cycle 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), bone marrow biopsies/aspirates will be required on Day 1 of Cycle 4 and every cycle thereafter until subject achieves CR, CRi, or MLFS.

    Note: In the event that the subject experiences prolonged PR or SD beyond Cycle 4/Day 1, less frequent bone marrow biopsy/aspirate assessments may be allowed after consultation with the Sponsor Medical Monitor.
- Beyond Cycle 4/Day 1, in subjects who achieve first CR, CRi or MLFS, perform bone marrow biopsies/aspirates on Day 1 of Cycle 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 at 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: Bone Marrow Biopsy/Aspirate Schedule for AML



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

7.1.2. Bone Marrow Biopsies/Aspirates (Subjects with High-risk MDS)

During the first 12 cycles:

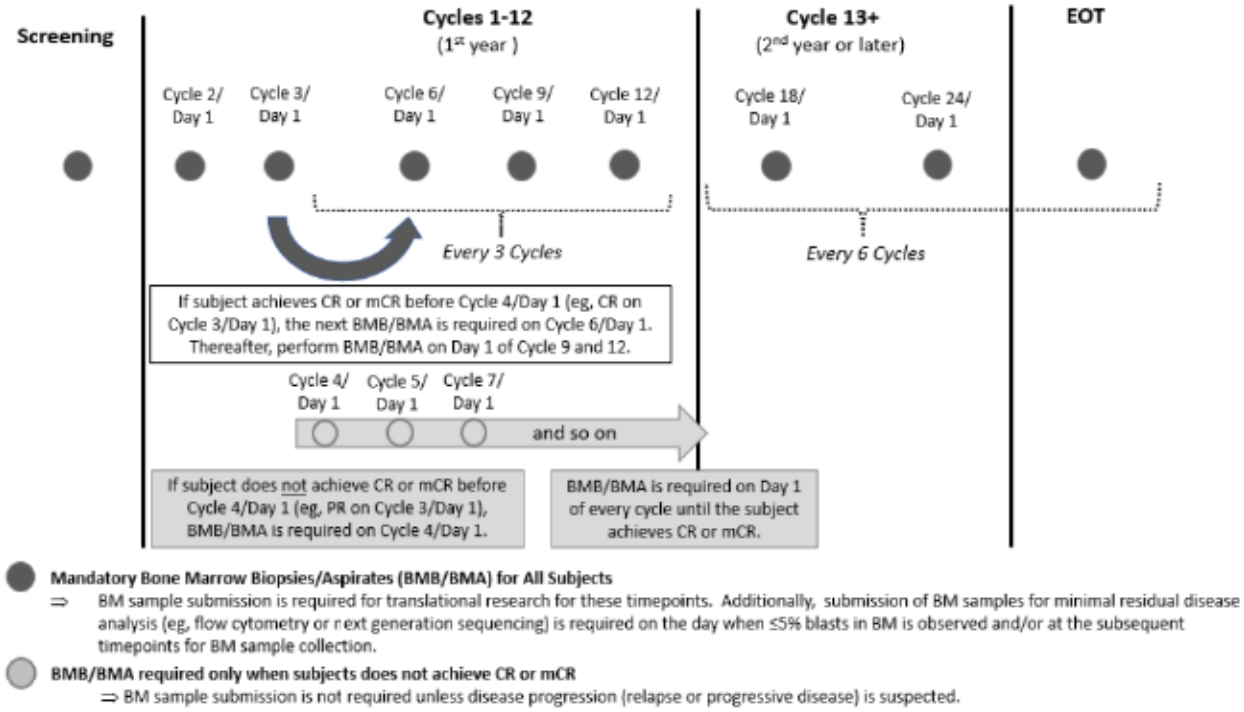
- Bone marrow biopsies/aspirates are mandated on Day 1 of Cycles 2 and 3 for all subjects.
  - If subject achieves CR or mCR before Cycle 4/Day 1 (eg, CR on Cycle 3/Day 1), bone marrow biopsies/aspirates will not be required on Cycle 4/Day 1.
    - Perform bone marrow biopsies/aspirates on Day 1 of Cycle 6, 9, and 12 if subject remains in CR or mCR.
  - If subject does not achieve CR or mCR before Cycle 4/Day 1 (eg, PR on Cycle 3/Day 1), bone marrow biopsies/aspirates will be required on Day 1 of Cycle 4 and every cycle thereafter until subject achieves CR or mCR in principle.

Note: In the event that the subject experiences prolonged PR or SD beyond Cycle 4/Day 1, less frequent bone marrow biopsy/aspirate assessments may be allowed after consultation with the Sponsor Medical Monitor.

- Beyond Cycle 4/Day 1, in subjects who achieve first CR or mCR, perform bone marrow biopsies/aspirates on Day 1 of Cycle 6, 9, and 12. For example:
  - If subject achieves first mCR on Cycle 5/Day 1, perform next bone marrow biopsies/aspirates on Cycle 6/Day 1.
  - If subject achieves first CR (without prior mCR) 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 or mCR on Cycle 12/Day 1, bone marrow biopsies/aspirates will be required at 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 7.2: Bone Marrow Biopsy/Aspirate Schedule for High-risk MDS



EOT = End-of-trial; BM = bone marrow; BMA = bone marrow aspirate; BMB = bone marrow biopsy; CR = complete remission; mCR = marrow complete remission; PR = partial remission

7.1.3. Bone Marrow Samples for Translational Research (AML and High-risk MDS)

Bone marrow samples for translational research need to be submitted at the following visits. Please see the instructions in the Laboratory Manual.

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

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

8.1. Pharmacokinetic Variables

The PK parameters for milademetan will include Cmax, Tmax, Ctrough, and AUC24h.

As an exploratory substudy, plasma AZA concentrations may be measured. The PK parameters for AZA will include Cmax, Tmax, and AUC6h.

Blood samples for PK analyses from subjects receiving single agent milademetan will be obtained at the time points specified in the Schedule of Events (Table 17.1) for subjects in the Dose Escalation part of the study.

During Dose Escalation of milademetan in combination with AZA, blood samples for the PK of milademetan will be collected at the Cycle 1 time points shown in Table 8.1 and Table 8.2 for the 2 dosing schedules.

Table 8.1: Cycle 1 Blood Sample Collection for Pharmacokinetics During Dose Escalation (Part 1A, Schedule E)

Days	5							6[a]	7[a]	14[a]							22
Hour	0[b]	0.5[c]	1[c]	2[c]	3[c]	4[c]	6-10	0[b]	0[b]	0[b]	0.5[c]	1[c]	2[c]	3[c]	4[c]	6-10	0[b]

[a] PK samples on these days will not be collected for subjects on the alternative (5+2) AZA schedule (Figure 3.3)
[b] Pre-dose within 30 minutes prior to drug administration
[c] ± 10 minutes

Table 8.2: Cycle 1 Blood Sample Collection for Pharmacokinetics During Dose Escalation (Part 1A, Schedule F)

Days	8							9	14[a]							22
Hour	0[b]	0.5[c]	1[c]	2[c]	3[c]	4[c]	6-10	0[b]	0[b]	0.5[c]	1[c]	2[c]	3[c]	4[c]	6-10	0[b]

[a] Day 14 PK samples will not be collected if subjects are treated with AZA in the 5+2 schedule.
[b] Pre-dose within 30 minutes prior to drug administration
[c] ± 10 minutes

There is minimal potential for DDI between AZA and milademetan based on in vitro data. However, this exploratory substudy (n = 6) may be used to exclude any possible DDI (ie, P-gp or BCRP inhibition by milademetan) since AZA and milademetan may be co-administered on Days 5 to 7. Preferentially, the first 6 subjects receiving milademetan on Day 5 will participate in this exploratory substudy. Blood samples will be collected at Cycle 1/Day 1 (AZA alone) and Cycle 1/Day 7 (AZA + milademetan) for potential measurement of plasma AZA concentrations as shown in Table 8.3. Plasma AZA concentrations may also be measured from samples collected for milademetan PK on Cycle 1/Day 5 (AZA + milademetan) as shown in Table 8.1.

Table 8.3: Cycle 1 Blood Sample Collection for Pharmacokinetics of 5-Azacitidine During Dose Escalation (n = 6, Milademetan on Days 5 to 14 – Part 1A, Schedule E)

Days	1 and 7					
Hour	0[a]	0.5[b]	1[b]	2[b]	3[b]	6[b]

[a] Pre-dose within 30 minutes prior to drug administration
[b] ± 10 minutes

During dose expansion of milademetan in combination with AZA, blood samples for the PK of milademetan will be collected at the Cycle 1 time points shown in Table 8.4.

Table 8.4: Cycle 1 Sparse Sample Collection for Milademetan Pharmacokinetics During Dose Expansion for All Subjects

Days	1st Day of Milademetan (Cycle 1/Day 5 or Day 8)[a]			2nd Day of Milademetan (Cycle 1/Day 6 or Day 9)[a]	Cycle 1/Day 14[a]	
Hour	0.5[b]	3[b]	6-10	0[c]	0[c]	3-6

[a] This PK sample collection is only applicable for Schedule e and Schedule f. The first and second days of milademetan dose are dependent on the dosing schedule chosen for Dose Expansion (ie, Days 5 and 6 if milademetan starts on Day 5 and Days 8 and 9 if milademetan starts on Day 8). PK samples, for Cycle 1/Day 6 and Day 14 will not be collected for subjects on the alternative (5+2) AZA schedule (Figure 3.3).
[b] ± 10 minutes
[c] Pre-dose within 30 minutes prior to drug administration

Additionally, samples may be obtained at any time during the study if deemed clinically necessary. At each time point, approximately 5 mL of blood will be collected. Instructions for the handling of blood samples and shipping of PK samples are included in a separate document (Laboratory Manual). The actual time of study drug administration and the exact time of blood sample collection must be recorded on the eCRF.

The PK samples will be shipped to a central laboratory for forwarding to a Sponsor-designated bioanalytical laboratory. Plasma concentrations of milademetan will be measured using a validated assay at the bioanalytical laboratory. Plasma concentrations of AZA will be measured using a validated assay, if determined important to exclude potential DDI.

8.2. Pharmacodynamic and Predictive Biomarker Variable(s)

8.2.1. Tumor Protein p53 Status

Confirmation of TP53 wild-type status is NOT required prior to milademetan and AZA dosing. If requested, the Investigator and subject may be informed about the genotyping result if the testing result shows that a subject's malignant cells contain a non-synonymous mutation, insertion, or deletion in the TP53 gene. If study treatment has already begun, the subject may choose to discontinue study treatment or continue study treatment as long as clinical benefit is noted per the Investigator's judgement. TP53 re-testing can be considered.

8.2.2. Pharmacodynamic Variables

Induction of serum MIC-1 will be assessed as a PDy biomarker. Serum samples will be collected at multiple time points in the study to assess the effect of milademetan treatment on MIC-1 induction.

8.2.3. Exploratory Biomarker Analysis

Leukemic cell enrichment:

Specimens of blood and bone marrow collected according to the Schedule of Events may be enriched for leukemic cells. After enrichment, the leukemic cells will be divided for preparation of RNA, DNA, and protein, or fresh-frozen to analyze TP53 genotype or other biomarkers.

Leukemic samples collected from blood and/or bone marrow may be examined for components of the p53 pathway in the form of multi-gene RNA and/or protein signature. Other biomarkers may include DNA analysis to determine gene mutations, copy number variations, and CpG methylation status. Additional biomarkers both inside and/or outside of the p53 pathway may be included in order to better understand the responsiveness to therapy. These may include protein, metabolite, gene expression, and genetic biomarkers.

8.3. Genetic and Pharmacogenomic Testing

As part of this study, a buccal swab will also be banked for possible future genetic and/or PGx analysis of germline DNA. The collected germline DNA will be used as a control to determine whether a gene mutation identified in the malignant cell DNA is unique to that DNA or whether the mutation was inherited. This DNA sample may also be used in a PGx analysis. These analyses may be run during the course of treatment or at the End-of-treatment. The sample will be stored until the time that it may be analyzed.

The buccal swab will be collected on Day 1 of Cycle 1 prior to study drug administration from all subjects in the study.

The results may also 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 AZA 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 and have their sample destroyed at any time.

The buccal swab will be shipped to a central laboratory for processing.

To ensure subject confidentiality, sample tubes will be identified only by a barcode label. This barcode will be linked to the subject's SID number.

Refer to the Study Manual for instructions for sample collection, preparation, handling, storage, and shipment.

9. SAFETY ASSESSMENTS

9.1. Adverse Events

All clinical AEs occurring after the subject signs the ICF and up to 30 days after the last dose of study drug during either Parts 1 and 1A or Part 2, whether observed by the Investigator or reported by the subject, will be recorded on the AE eCRF 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 SAEs are to be reported according to the procedures in Section 9.4. Always report 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 which do not worsen in severity should not be reported as SAEs (see Section 9.3.2 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 or SAE. However, when a subject dies from disease progression with no other immediate causes, "disease progression" should be reported as an SAE. In addition, 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.

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 discovered 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. All laboratory values must be appraised by the Investigator as to clinical significance. All post-baseline abnormal laboratory values considered clinically significant by the Investigator must be recorded as an AE on the eCRF, and if serious, must be reported as an SAE following the procedures in Section 9.4.

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.

9.2. Events of Special Interest

Not applicable.

9.3. Definitions

9.3.1. Adverse Event

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which 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 (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

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

9.3.2. Serious Adverse Event

An SAE is defined as 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.
- Is an important medical event.

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the 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:

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

9.3.3. Adverse Event Severity

All AEs will be graded (1 to 5) according to the NCI-CTCAE Version 5.0 (Version 4.03 before 01 Apr 2018):

- Grade 1 Mild AE.
- Grade 2 Moderate AE.
- Grade 3 Severe AE.
- Grade 4 Life-threatening or disabling AE.
- Grade 5 Death related to AE.

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

9.3.4. Causality Assessment

The Investigator should assess causal relationship between an AE and milademetan or AZA on the basis or his/her clinical judgment and the following definitions. The causality assessment should be made based on the available information and can be updated as new information becomes available.

- 1 = Related:

  The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

  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.

- 2 = Not Related:

  The AE does not follow a reasonable sequence from study product administration, or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

9.3.5. Action Taken Regarding the Study Drug

- 1 = None: No change in study drug dosage was made.
- 2 = Discontinued Permanently: The study drug was permanently stopped.
- 3 = Reduced: The dosage of study drug was reduced.

- 4 = Interrupted: The study drug was temporarily stopped.

9.3.6. Adverse Event Outcome

- 1 = Recovered/Resolved.

  The subject fully recovered from the AE with no residual effect observed.
- 2 = Recovered/Resolved with Sequelae.

  The residual effects of the AE are still present and observable.

  Identify sequelae/residual effects.
- 3 = Not Recovered/Not Resolved.

  The AE itself is still present and observable.
- 4 = Fatal.
- 5 = Unknown.

9.3.7. Other Action Taken for Event

- 1 = None.

  No treatment was required.
- 2 = Medication required.

  Prescription and/or over the counter medication was required to treat the AE.
- 3 = Hospitalization or prolongation of hospitalization required.

  Hospitalization was required or prolonged due to the AE, whether or not medication was required.
- 4 = Other.

9.4. Serious Adverse Event Reporting Procedure for Investigators

9.4.1. Initial Reports

Within 24 hours of receipt of an SAE report:

- Call Medpace study personnel immediately to report the SAE.

  Safety Contact Information:
  Medpace Clinical Safety
  Medpace SAE hotline - US:
  PPD
- Complete a Daiichi Sankyo Serious Adverse Event Report (SAVER) form, sign it, and fax it to Medpace using the designated fax transmittal form. Medpace will

review and forward the SAVER form to Daiichi Sankyo Clinical Safety and Pharmacovigilance (CSPV) PPD .

- Call the Medpace SAE hotline for any questions regarding SAE reporting.
- Place the initial version of SAVER in the subject's file.

9.4.2. Follow-up Reports

This is for NEW information received on a previously reported SAE.

Within 24 hours of the receipt of new information for a reported SAE:

- Complete a Daiichi Sankyo SAVER form with the new information. Please complete Sections 1 through 3 even if they contain no new information. For Sections 4 through 10, provide only the new information. Sign and fax the form to Medpace using the fax transmittal form.
- For SAEs that resulted in death, provide the autopsy report via e-mail, fax, or express mail.
- Medpace will review and forward the follow-up SAVER form and supporting documents to Daiichi Sankyo CSPV PPD .
- Place the follow-up version of the SAVER form and all supporting documentation in the subject's file.

9.4.3. Notifying Regulatory Authorities, Investigators, and Institutional Review Board/Ethics Committees

Daiichi Sankyo and/or Medpace will inform Investigators and regulatory authorities of any Suspected Unexpected Serious Adverse Event Reactions (SUSARs) occurring in other study centers or other Daiichi Sankyo studies of the study drug, as appropriate per local reporting requirements.

In the US, it is the Investigator's responsibility to inform the IRB upon receipt of the Sponsor's notification of SUSARs that occurred with the study drug.

9.5. 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 17.1). If required by local regulations, additional pregnancy tests will be performed.

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 an 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 as outlined in Section 9.4.

9.6. Clinical Laboratory Evaluations

The following clinical laboratory tests will be performed:

- Hematology variables include RBC count, hemoglobin, hematocrit, platelet count, and WBC count with 5-part differential, including ANC and reticulocyte count.
- Serum chemistry variables include sodium, potassium, bicarbonate, chloride, calcium, magnesium, phosphorus, albumin, glucose, serum creatinine, uric acid, total protein, BUN, AST, ALT, alkaline phosphatase, and total and direct bilirubin.
- Serum pregnancy test.

All laboratory values must be appraised by the Investigator as to clinical significance. All abnormal laboratory values considered clinically significant by the Investigator must be recorded in the AE page of the eCRF. Abnormal laboratory values (NCI-CTCAE Grade 3 or 4) occurring during the clinical study will be followed until repeat test results return to normal (or baseline), stabilize, or are no longer clinically significant.

9.7. Vital Signs

Vital sign measurements will include systolic blood pressure, diastolic blood pressure, respiratory rate, pulse rate, and body temperature.

9.8. Electrocardiograms

Standard supine 12-lead ECGs will be performed by qualified technicians in triplicate as noted in the Schedule of Events. Electrocardiograms will be reviewed at the site for treatment of any urgent issues. The clinical significance of any ECG change must be assessed by the Investigator in the context of the subject's medical history, physical examination, and concomitant medications. The Investigator or delegated physician will review, sign, and date all ECGs.

9.9. Physical Findings

Physical examinations will evaluate the following body systems/organs: general appearance; dermatological; head and eyes; ears, nose, mouth, and throat; pulmonary; cardiovascular; abdominal; genitourinary (optional); lymphatic; musculoskeletal/extremities; and neurological. Weight and height will be recorded in kilograms and centimeters, respectively.

9.10. Other Safety Assessments

Not applicable.

10. OTHER ASSESSMENTS

Not applicable.

11. STATISTICAL METHODS

11.1. Analysis Sets

The following analysis sets will be defined in this study:

- Enrolled Analysis Set will include all subjects who sign the ICF and meet inclusion/exclusion criteria.
- Safety Analysis Set (and Full Analysis Set) will include all enrolled subjects who received at least 1 dose of milademetan or AZA.
- DLT-evaluable Set will include all subjects enrolled in the Dose Escalation part who had a DLT within Cycle 1 (28 days) on the study, or who did not have a DLT but received at least 75% scheduled dose of milademetan and AZA and completed the Cycle 1 evaluation.
- PK Analysis Set will include all subjects in the Safety Analysis Set who had measurable plasma concentration data to characterize the PK profile of milademetan or AZA.

11.2. General Statistical Considerations

The primary analysis is to assess the safety and tolerability of milademetan alone and in combination with AZA in subjects with AML or high-risk MDS.

The data cut-off for the primary analysis will occur after all subjects have either discontinued the study or completed at least 6 cycles of treatment. After the primary analysis, the main study will be closed. After the data cut-off date for primary analysis, data of interest will be collected and analyzed (if deemed necessary) for subjects who are still benefiting from the study drug until study completion.

Descriptive statistics will be provided for selected demographic, safety, PK, and PDy data by dose cohort at each timepoint as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges, 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 and biomarker 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 from the Dose Escalation part will be summarized by dose level of milademetan alone and in combination with AZA and overall.

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.

11.3. Study Population Data

Disposition and reasons for ending the treatment and discontinuing from the study will be summarized and listed for subjects in the Safety 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

For AML, the secondary endpoints of efficacy will include the rates of CR, CRi, CRc, MLFS, PR, SD, ORR, and DOR according to Investigator assessment (Section 2.3.3). For Part 1 and 1A only, treatment failure rate is included whereas SD is not included. Stable disease rate will be summarized when SD has persisted for at least 3 months. Additionally, CRh rate will be evaluated separately from the abovementioned responses.

For subjects with MDS, the efficacy endpoints will be CR rate, mCR rate, PR rate, cytogenic response, SD rate, disease progression, transfusion independence, and OS. Additionally, hematological improvement will be evaluated separately from the abovementioned responses.

The efficacy endpoints will be listed and summarized using descriptive statistics based on the FAS by dose for the combined Dose Escalation and Dose Expansion parts.

Transplantation rate and transfusion independency will be based on data reported by study sites.

For response rates (eg, 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 Analyses

11.5.1. Pharmacokinetic Analyses

Plasma concentration data for milademetan and/or AZA will be summarized using descriptive statistics by dose cohort at each timepoint.

For Dose Escalation, the PK parameters Cmax, Tmax, and AUC24h for milademetan on Day 1 for single agent treatment (or Day 5 or Day 8 depending on the dose schedule in combination treatment with AZA) and Day 15 for single agent (or Day 14 in combination treatment with AZA, excluding subjects that are treated with AZA in the 5+2 schedule) of Cycle 1 and Ctrough on multiple visit days will be calculated using non-compartmental analysis.

For Dose Expansion, only sparse PK samples will be collected. These data will be analyzed using PopPK methods.

AZA concentration samples will be collected at Cycle 1/Day 1 (AZA alone) and at Cycle 1/Day 7 (AZA + milademetan) as an exploratory substudy in 6 subjects. The PK parameters Cmax, Tmax, and AUC6h for AZA will be summarized by treatment using descriptive statistics.

A PopPK analysis and exposure-response analyses for various endpoints may be developed. If developed, then the PopPK plan and the Technical Report will be provided separately.

11.5.2. Pharmacodynamic Analyses

Changes in MIC-1 levels in serum and other PDy parameters, if available, will be listed and summarized using descriptive statistics by dose level cohort.

11.5.3. Biomarker and Exploratory Analyses

Explorative analyses for potential biomarkers that may be predictive of benefit from milademetan and AZA will be graphed and/or listed and summarized using descriptive statistics by dose level 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 SAEs, TEAEs, 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 will be categorized using MedDRA Version 17.0. Adverse events and laboratory test results will be graded according to the NCI-CTCAE Version 5.0 (Version 4.03 before 01 Apr 2018). In the Dose Escalation part, the incidence of DLTs will also be evaluated.

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 among the DLT-evaluable subjects in the DLT-evaluable set will be listed and summarized for each dose of milademetan alone and in combination with AZA.

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 days after the last dosing date), having been absent at pre-treatment; reemerges 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 or AZA.

A by-subject AE (including TEAE) data listing will be provided including, but are 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, will be listed.

11.6.2. Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for selected clinical laboratory test results (hematology and blood chemistry) 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 (Version 4.03 before 01 Apr 2018), if applicable. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-treatment value according to the NCI-CTCAE grade, will be provided for selected clinical laboratory tests. Abnormal clinical laboratory test results that are deemed of clinical significance or are Grade 3 or 4 will be listed.

11.6.3. Vital Signs 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, HR, 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 QTcF will be calculated as follows: $QTcF = QT/(RR)^{1/3}$.

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. Physical Examination Finding Analyses

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

11.6.6. Other Safety Analyses

The ECOG performance status at baseline will be summarized for the Safety Analysis Set. A shift table, presenting the 2-way frequency tabulation for Baseline and End-of-treatment Visit, will be provided for ECOG performance status.

11.7. Other Analyses

Not applicable.

11.8. Interim Analyses

No formal interim analysis is planned, except for the assessment of the MTD after each escalation cohort in the Dose Escalation part.

11.9. Data and Safety Monitoring Board

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. Cohorts of at least 3 DLT-evaluable subjects per dose level will be enrolled in the Dose Escalation part. As an exception, the model will be reevaluated before enrollment of any additional subjects to the cohort if 2 evaluable subjects in the cohort experience a DLT before the enrollment of the next subject. For a subject to be considered evaluable for dose escalation decisions, the subject must have received at least 75% of the prescribed doses within the DLT observation period in Cycle 1 or experienced a DLT in Cycle 1. Subjects who are unable to complete at least 75% of prescribed doses of milademetan or AZA within the DLT observation period as a result of unequivocal progression of disease may be replaced.

In Dose Escalation (Part 1 and Part 1A), approximately 80 evaluable subjects may be enrolled to estimate the MTDs of milademetan as a single agent and in combination with AZA and to identify RDE.

In Dose Expansion (Part 2) there will be 3 cohorts: Cohort 1 (subjects with R/R AML), Cohort 2 (subjects with newly diagnosed AML unfit for intensive chemotherapy), and Cohort 3 (subjects with high-risk MDS). Simon 2-stage optimal/minimax design will be used to implement a futility stop given a 1-sided type 1-error rate of 10% and 80% of power. Approximately 40 subjects per cohort (approximately 120 subjects in total) will be enrolled:

- Cohort 1 (R/R AML): Hypotheses regarding the rates (CR/CRi plus MLFS) for the combination to be tested are H_0: $p < 20\%$ and H_1: $p > 35\%$. At stage 1, if CR/CRi plus MLFS has been achieved as the best response in less than 5 subjects out of 22 evaluable subjects, enrollment will be stopped. Otherwise, the enrollment for stage 2 will be completed with an addition of 19 subjects (for a total of 41 subjects evaluable for best response in both stage 1 and stage 2).
- Cohort 2 (newly diagnosed AML unfit for intensive chemotherapy): Hypotheses regarding the rates (CR/CRi plus MLFS) for the combination to be tested are H_0: $p < 15\%$ and H_1: $p > 30\%$. At stage 1, if CR/CRi plus MLFS has been achieved as the best response in less than 4 subjects out of 19 evaluable subjects, enrollment will be stopped. Otherwise, the enrollment for stage 2 will be completed with an addition of 20 subjects (for a total of 39 subjects evaluable for best response in both stage 1 and stage 2).
- Cohort 3 (high-risk MDS): Hypotheses regarding the rates (CR, mCR, and PR) for the combination to be tested are H_0: $p < 15\%$ and H_1: $p > 30\%$. At stage 1, if CR, mCR, and PR have been achieved as the best response in less than 4 subjects out of 19 evaluable subjects, enrollment will be stopped. Otherwise, the enrollment for stage 2 will be

completed with an addition of 20 subjects (for a total of 39 subjects evaluable for best response in both stage 1 and stage 2).

11.11. Specification of Bayesian Logistic Regression Model with Escalation with Overdose Control

11.11.1. 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:

$\text{logit}(\pi(d)) = \log(\alpha) + \beta \log(d/d^*), \quad \alpha > 0, \beta > 0$

where $\text{logit}(\pi(d)) = \ln(\pi(d)/(1-\pi(d)))$, $\pi(d)$ is the probability of a DLT or the DLT rate at dose d. Doses are rescaled as d/d* with the reference dose d* = 120 mg/day. As a consequence, α is equal to the odds of toxicity at d*. Note that for a dose equal to zero, the probability of toxicity is zero.

11.11.2. Prior Specification for Bayesian Logistic Regression Model Parameters

The Bayesian approach requires the specification of a prior distribution for the BLRM parameters. A minimally-informative bivariate normal prior[13] for the model parameters $(\log(\alpha),\log(\beta))$ is obtained as follows:

- Based on the DLT data from the ongoing solid tumor or lymphoma study (DS3032-A-U101), there are 13 DLT-evaluable subjects and 3 DLTs from 6 dose cohorts (# DLT/# subjects): 15 mg (0/2), 30 mg (0/1), 60 mg (0/1), 120 mg (0/3), 160 mg (2/5), and 240 mg (1/1) as of 25 Apr 2014. The median posterior probabilities of DLT are calculated to be 7.0%, 19.7%, 31.4%, and 49.0% at 60 mg, 120 mg, 160 mg, and 240 mg, respectively.
- For the remaining doses, the medians of probability of DLT are assumed linear in log-dose on the logit-scale.
- Based on the above medians for the probability of DLT at each dose and wide prior credible intervals (obtained from minimally informative Beta distributions), the optimal parameters of the bivariate normal distribution can be obtained as follows:

Parameters	Means	Standard Deviations	Correlation
$\log(\alpha)$, $\log(\beta)$	(-1.4165, 0.1849)	(2.0487, 1.0892)	-0.5669

Prior specification for alternative schedules of milademetan as a single agent and in combination with AZA will be updated/derived using ongoing DLT data from existing dose schedules.

11.11.3. 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 doses in the qd 21/28 schedule: 60, 80, 120, 160, 200, 240, 300, and 360 mg/day. After a minimum of 3 subjects of each cohort completes the DLT evaluation during Cycle 1, the posterior distributions of the DLT rate will be 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 4 intervals at each dose level ([0%, 16%) as the DLT rate interval for underdosing, [16%, 33%) as the target DLT rate interval, [33%, 60%) as the DLT rate interval for excessive toxicity, and [60%, 100%] as the DLT rate interval for unacceptable toxicity) will be calculated and used for dose recommendation for the next cohort according to the EWOC principle. The above provisional doses are based on dose escalation in the solid tumor or lymphoma study (Study DS3032-A-U101). 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% (Section 3.1.2).

The EWOC principle requires that the BLRM 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 less than 25% of probability for the DLT rate >33% [probability for excessive or unacceptable toxicity]).

12. DATA INTEGRITY AND QUALITY ASSURANCE

The Investigator/investigational site will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

12.1. Monitoring and Inspections

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

The monitor is responsible for visiting site(s) at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH GCP and local regulations on the conduct of clinical research. The monitor is responsible for inspecting the eCRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs.

The monitor will communicate deviations from the protocol, SOPs, GCP, and applicable regulations to the Investigator and will ensure that appropriate action 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 and documented.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor. Inspection of site facilities (eg, pharmacy, drug storage areas, laboratories etc.) 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.

12.2. Data Collection

Electronic case report form completion should be kept current to enable the monitor to review the subject's status throughout the course of the study. The eCRFs will be completed, reviewed, and signed off or e-signed by the Investigator as described in the Data Management Plan and in the monitoring plan for Clinical Research Associates. Instructions for completion of the eCRFs will be provided. Corrections to electronic forms will be automatically documented by using the software's "audit trail".

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.3. Data Management

This is an open-label study. Each subject will be identified in the database by a unique SID as defined by the Sponsor.

To ensure the quality of clinical data across all subjects and 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 eCRFs, 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 electronic data capture (EDC) application. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. 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.

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

All prior cancer therapy and prior/concomitant medications entered into the database will be coded by using the latest version of World Health Organization Drug Dictionary. All AEs will be coded by using MedDRA Version 17.0.

12.4. Study Documentation and Storage

The Investigator will maintain a Signature List of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on eCRFs will be included on the Signature List.

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include, but are not limited to, hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (Trial Master File) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Essential documents include:

- Subject files containing completed eCRFs, ICFs, and supporting copies of source documentation (if kept).
- Study files containing the protocol with all amendments, IBs, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the IRB and the Sponsor.
- Records related to the study drug(s) including acknowledgment of receipt at site, accountability records and final reconciliation and applicable correspondence.

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

12.5. Record Keeping

Records of subjects, source documents, monitoring visit logs, data correction forms, eCRFs, inventory of study product, regulatory documents (eg, protocol and amendments, IRB correspondences and approvals, approved and signed ICFs, Investigator's Agreement, clinical supplies receipts, distribution and return records), and other Sponsor correspondence pertaining to the study must be kept in appropriate study files at the site. 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 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.

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 the Sponsor. This agreement will include the financial information agreed upon by the parties.

13.2. Reimbursement, Indemnity, and Insurance

Reimbursement, indemnity, and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

14. PUBLICATION POLICY

A study site may not publish results of a study until after a coordinated multicenter publication has been submitted or until 1 year after the study has ended, whichever occurs first. Therefore, the study site will have the opportunity to publish the results of the study, provided that the Sponsor has had the opportunity to review and comment on the study site's proposed publication prior to its being submitted for publication with the prior advice of DSI Legal Affairs (intellectual property council) and with proper regard to the protection of subjects' identities.

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 Conference on Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), US Food and Drug Administration GCP Regulations: Code of Federal Regulations (CFR) Title 21, Parts 11, 50, 54, 56, and 312, as appropriate, and other applicable local regulations.

15.1.1. Subject Confidentiality

The Investigators and the Sponsor, Daiichi Sankyo, Inc. (DSI), will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

The Investigator must ensure that the subject's anonymity is maintained. On the electronic case report forms (eCRFs) or other documents submitted to the Sponsor and/or its contract research organization (CRO, Medpace) designee ("Agent" or CRO), subjects should be identified by a unique subject identifier as designated by the Sponsor. Documents that are not for submission to the Sponsor and/or the CRO (eg, signed ICFs) should be kept in strict confidence by the Investigator.

In compliance with applicable local guidelines and 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 direct access to review the subject's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above named representatives without violating the confidentiality of the subject.

15.1.2. Informed Consent Procedure

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study, and before any protocol-specific screening procedures or any study drugs are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical 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 IRB prior to being provided to potential subjects.

The subject's written informed consent should be obtained prior to his/her participation in the study, and should be documented in the subject's medical records, as required by 21 CFR Part 312.62. The ICF should be signed and personally dated by the subject or a legally acceptable representative 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 or legal representative. The date and time (if applicable) that informed consent was given should be recorded on the eCRF.

If the subject or legally acceptable representative cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICF after the subject or the legally acceptable representative has orally consented to the subject's participation and, if possible, signed the ICF. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequately explained to and apparently understood by the subject or the legally acceptable representative and that informed consent was freely given by the subject or the legally acceptable representative.

Suggested model text for the ICF for the study and any applicable subparts (genomic, PK, etc.) and assent forms for pediatric subjects (if applicable) are provided in the DSI ICF template for the Investigator to prepare the documents to be used at his or her site. Updates to applicable forms will be communicated via letter from the Clinical Study Manager.

The consent for genetic and pharmacogenomic (PGx) sampling for buccal swab and blood and/or bone marrow biopsies/aspirates should be documented in the subject's written informed consent. The consent form should be signed and personally dated by the subject or the subject's legally acceptable representative prior to his/her participation in the study.

Predictive biomarkers will be analyzed with the intent of identifying subjects who will most likely derive clinical benefit from treatment with milademetan. The following candidate-predictive biomarkers are currently envisaged (other predictive biomarkers in addition to or in place of these may be considered as suggested by emerging information): components of the p53 pathway in the form of multi-gene and/or protein signature which may include, but are not limited to, p53, p21, p14, p16, MDM2, murine double minute 4 (MDM4), and cyclin-dependent kinase inhibitor 2A (CDKN2A) copy number. These predictive biomarkers will be assessed in blood samples, bone marrow samples (archived or recent biopsies/aspirates), and/or other collected samples, using assays that have been established or are being established. Further exploratory studies may be performed on tissue, soluble, or genomic biomarkers based on emerging scientific knowledge to better understand the target disease, the effects of study treatment, and potential mediators of primary and acquired resistance to therapy.

15.1.3. Regulatory Compliance

The study protocol, subject information and consent form, the IB, any subject diary card or written instructions to be given to the subject, available safety information, subject recruitment procedures (eg, advertisements), information about payments and compensation available to the subjects, and documentation evidencing the Investigator's qualifications should be submitted to the IRB for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the SAP.

The Investigator must submit and, where necessary, obtain approval from the IRB and/or DSI for all subsequent protocol amendments and changes to the informed consent document or changes of the investigational site, facilities, or personnel. The Investigator should notify the IRB of deviations from the protocol or SAEs occurring at the site and other AE reports received from the Sponsor and/or the CRO, in accordance with local procedures.

As required by local regulations, the Sponsor's local Regulatory Affairs group will ensure approval from the appropriate regulatory authorities is obtained prior to study initiation and that relevant regulatory authorities receive appropriate notification of, or if necessary, approve, substantive changes to the initial protocol.

15.2. Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the Investigator by the Sponsor or the CRO. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB within 5 working days. The Sponsor will assure the timely submission of amendments to regulatory authorities.

15.3. Address List

15.3.1. Sponsor

Daiichi Sankyo, Inc.
211 Mt. Airy Road
Basking Ridge, NJ 07920-2311
PPD

15.3.1.1. Sponsor's Medical Monitor

PPD
Senior Director, Global Oncology Research and Development
PPD

15.3.1.2. Sponsor's Clinical Scientist

PPD
Senior Director, Global Oncology Research and Development
Daiichi Sankyo Pharma Development
PPD

15.3.1.3. Sponsor's Clinical Study Manager/Delivery Lead

PPD
Sr. Clinical Study Manager, Clinical Development Operations
PPD

15.3.1.4. Sponsor's Safety Contact

PPD
Senior Director, Clinical Safety and Pharmacovigilance
PPD

15.3.1.5. Sponsor's Biostatistician

PPD
Director, Biostatistics and Data Management
PPD

15.3.2. CRO

Medpace, Inc.
5375 Medpace Way
Cincinnati, OH 45227
PPD

15.3.2.1. CRO Medical Monitor

PPD
Vice President, Medical Affairs
PPD

15.3.2.2. CRO Project Manager

PPD
Clinical Trial Manager
PPD

15.3.2.3. CRO Drug Safety

PPD

15.3.2.4. CRO Data Management

PPD

15.3.3. Biological Specimens

TP53 Genotyping

PPD

LabCorp Clinical Trials (formerly Covance Genomics Laboratory)
401 Terry Avenue N, Suite 200
Seattle, WA 98109

PPD

MIC-1 Test

PPD

Medpace Reference Laboratory
5365 Medpace Way
Cincinnati, OH 45227

PPD

15.3.4. Bioanalytical Laboratory

PPD

Advion Bioanalytical Labs
A Quintiles Company
19 Brown Road
Ithaca, NY 14850

PPD

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17. APPENDICES

17.1. Schedule of Events

Table 17.1: Schedule of Events Part 1 (Dose Escalation) – Milademetan as a Single Agent

Cycle[a]	Pre-Cycle	1																2		3	4 +	Post-Cycle	
Visit Number	1	2							3	4	5							6	7	8	9	10 +		
Visit Description	SCR	EX and 1st Dose							EX	EX	EX							EX	EX	EX	EX	EX	EOT[b]	F/U[c]
Cycle Day(s)	-14 to 0	1[d]							2	8	15							22[e]	1	15	1	1	ND	ND
Visit Window (days)										± 2	± 2							± 2	± 4	± 4	± 4	± 4	± 5	
Time post-dose (hours)		Pre-dose	1	2	3	6	8	10			Pre-dose	1	2	3	6	8	10							
Informed consent	X																							
Assign SID number	X																							
Demographics/medical history	X																							
Inclusion/exclusion criteria	X																							
Pregnancy test[f]	X																				X		X	
Adverse events	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	
ECOG	X	X								X	X							X	X	X	X	X	X	
Height	X																						X	
Physical examination, including weight	X	X								X	X							X	X	X	X	X	X	
Vital signs[g]	X	X		X					X	X	X							X	X	X	X	X	X	
Safety laboratory[h]	X	X							X	X	X							X	X	X	X	X	X	
ECG (12-lead)[i]	X	X		X					X	X	X							X	X	X	X		X	
Bone marrow biopsy/aspirate[j]	X										X								X[k]	X[k]	X	X		
Buccal swab		X																						
Biomarker blood sample[l]		X							X	X									X				X	
Milademetan administration[m]		X							X	X	X								X	X	X	X		
Blood sample for PK measurement[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X	
MIC-1 serum sample[o]		X				X			X	X	X							X						
Dispense milademetan									X	X	X								X	X	X	X		
Pill diaries dispensed/reviewed									X	X	X							X	X	X	X	X	X	
Bone marrow re-biopsy/aspirate[p]																							X	
Record reason for discontinuation																							X	
Follow-up survival data[q]																							X	X

CR = complete remission; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End-of-treatment; EX = exam; MIC-1 = macrophage inhibitory cytokine-1; ND = not determined; PD = progressive disease; PK = pharmacokinetics; PR = partial remission; qd = once daily; qd 3/14 × 2 = qd for 3 of 14 days repeated twice in a 28-day cycle; qd 7/28 = qd on Days 1 to 7 of a 28-day cycle; qd 14/28 = qd on Days 1 to 14 of a 28-day cycle; qd 21/28 = qd on Days 1 to 21 of a 28-day cycle; SCR = Screening; SID = subject identification number; TBD = to be determined.

[a] Each cycle will last 28 days. Cohort safety assessment for DLTs will be performed after Day 28 of Cycle 1.
[b] EOT Visit will occur at the earliest day possible within 30 days after the last administration of milademetan. If the subject begins another form of anticancer therapy before the end of the 30-day period, every effort should be made to complete all 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] If the SCR Visit for Part 1 is performed within 24 hours of Cycle 1/Day 1, the assessments performed during SCR do not need to be repeated.
[e] For subjects in the qd 7/28 schedule, this visit is not needed, but safety evaluations (ie, everything but sampling for PK measurement and MIC-1) will be done if the subject presents with AEs of ≥Grade 3 on Day 15.
[f] Pregnancy test (serum) will be performed in female subjects of childbearing potential at SCR, Cycle 3/Day 1, and EOT Visit.
[g] Vital sign measurements will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature.
[h] Safety laboratory samples for Day 1 pre-dose (hematology, serum chemistry, and coagulation profile) can be collected within 72 hours before the first dose. Coagulation profile will be performed at SCR, Cycle 1/Day 1, Cycle 2/Day 1, EOT, and other visits as clinically indicated. Creatinine clearance will be performed at SCR.
[i] Electrocardiograms will be performed pre-dose unless specified, and at indicated post-dose time points on Cycle 1/Day 1. Procedure window is ± 1 hour. When there is a PK sample collection corresponding to the time point for ECGs, the ECG should be performed within 10 minutes prior to PK sample collection. Other unscheduled ECGs may be performed as clinically indicated. Electrocardiograms will be performed in triplicate.
[j] All unscheduled bone marrow assessments of disease burden performed on non-visit days must be reported as unscheduled visits. Bone marrow samples on Cycle 1/Day 15 are optional.
[k] If bone marrow aplasia is observed on Cycle 2/Day1, study drug will be withheld and a confirmation bone marrow assessment will be performed in 2 weeks.
[l] Blood samples drawn pre-dose of Cycle 1/Day 1, Day 2, and Day 8; Cycle 2/Day 1; and EOT Visit for biomarker analysis.
[m] For dose schedules: qd 21/28; qd 7/28; qd 3/14 × 2; or qd 14/28, milademetan is taken on Days 1 to 21; 1 to 7, 1 to 3 and 15 to 17; or 1 to 14, respectively. Milademetan is administered per protocol, at the clinical site at the indicated time.
[n] Blood samples for PK measurement will be collected pre-dose at the indicated visits (Cycle 1/Days 1, 2, 8, 15, and 22). Subjects will be instructed not to take their dose until after the sample has been collected on clinic days. Additional samples will be collected at the indicated time points. Post-dose PK samples will not be collected for subjects in the qd 7/28 and qd 14/28 schedules. The window for sample collection will be ± 15% of the specified time. Based on the PK profile established from the initial subjects treated in the study, sample collection time points may be modified upon notification by the Sponsor.
[o] Serum for MIC-1 induction will be obtained at the indicated time points (pre-dose and 6 hours post-dose on Cycle 1/Day 1 and pre-dose on Cycle 1/Days 2, 8, 15, and 22).
[p] A bone marrow re-biopsy or aspirate will be performed within 30 days of the last dose of study drugs, preferably prior to initiating new anticancer therapy, in subjects who have achieved an initial CR or PR but later developed PD while on therapy.
[q] If feasible, collect subject survival status, date and cause of death (if applicable), subsequent anticancer therapy, and HCT and HCT-relevant information (if performed).

Table 17.2: Schedule of Events Part 1A (Dose Escalation) and Part 2 (Dose Expansion) – with Milademetan on Days 5 to 14 (Schedule E)

Cycle[a]	Pre-Cycle	1															2			3		4 +		Post-Cycle	
Visit Number	1	2						3-8	9							10	11	12-18	19	20	21-27	28	29 +			
Visit Description	SCR	EX						EX	EX						EX	EX	EX	EX	EX	EX	EX	EX	EX	EX	EOT[b]	F/U[c]
Cycle Day(s)	-14 to 0	1[d]						2-4	5						6-7[e]	14[e]	22	1-4[f]	5-7 [e,g]	15	1-4[f]	5-7 [e,g]	1-4[f]	5-7 [e,g]	ND	ND
Visit Window (days)																± 2	± 2	± 4	± 4		± 4		± 4		± 5	
Time post-dose (hours)		Pre-dose	0.5	1	2	3	6		Pre-dose	0.5	1	2	3	4	6-10											
Informed consent	X																								
Assign SID number	X																								
Demographics/medical history	X																								
Inclusion/exclusion criteria	X																								
Pregnancy test[h]	X																				X			X	
Follicle stimulating hormone test[i]	X																								
Adverse events	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
Record transfusion	X[j]	X						X	X						X	X	X	X	X	X	X	X	X	X		
ECOG	X	X							X							X	X	X		X	X		X		X	
Height	X																								X	
Physical examination, including weight	X	X							X							X	X	X		X	X		X		X	
Vital signs[k]	X	X			X			X	X						X	X	X	X	X	X	X	X	X	X	X	
Safety laboratory[l]	X	X													X	X	X	X	X	X	X	X	X		X	
ECG (12-lead)[m]	X	X			X				X[n]			X	X[n]	X	X	X[n]	X	X		X	X				X	
Echocardiogram/MUGA[o]	X																									
Bone marrow biopsy/aspirate[p]	X																	X[q]		X[q]	X		X			
Buccal swab		X																								

Cycle[a]	Pre-Cycle	1													2			3		4 +		Post-Cycle	
Visit Number	1	2						3-8	9						10	11	12-18	19	20	21-27	28	29 +			
Visit Description	SCR	EX						EX	EX						EX	EX	EX	EX	EX	EX	EX	EX	EX	EOT[b]	F/U[c]
Cycle Day(s)	-14 to 0	1[d]						2-4	5						6-7[e]	14[e]	22	1-4[f]	5-7 [e,g]	15	1-4[f]	5-7 [e,g]	1-4[f]	5-7 [e,g]	ND	ND
Visit Window (days)																± 2	± 2	± 4	± 4		± 4		± 4		± 5	
Time post-dose (hours)		Pre-dose	0.5	1	2	3	6		Pre-dose	0.5	1	2	3	4	6-10											
Biomarker blood sample[r]		X							X							X	X	X		X	X		X		X	
AZA administration		X						X	X							X		X	X		X	X	X	X		
Milademetan administration[s]									X							X	X			X			X		
Blood sample for PK measurement (AZA)[t]		X[u]	X[u]	X[u]	X[u]	X[u]	X[u]		X	X[v]	X	X	X[v]	X	X[v]	X[u,v]	X[v]	X								
Blood sample for PK measurement (milademetan)[t]									X	X[v]	X	X	X[v]	X	X[v]	X[u,v]	X[v]	X			X					
Blood sample for banking plasma[w]		X															X				X		X		X[x]	
MIC-1 serum sample[y]		X							X						X		X	X		X						
Dispense milademetan																X			X			X				
Pill diaries dispensed/reviewed																X	X		X	X		X		X		
Bone marrow re-biopsy/aspirate[z]																									X	
Record reason for discontinuation																									X	
Follow-up survival data[aa]																									X	X

AZA = 5-azacitidine; CR = complete remission; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End-of-treatment; EX = exam; MIC-1 = macrophage inhibitory cytokine-1; MUGA = multigated acquisition; ND = not determined; PD = progressive disease; PK = pharmacokinetics; PR = partial remission; qd = once daily; SCR = Screening; SID = subject identification number; TBD = to be determined.

[a] Each cycle will last 28 days. Cohort safety assessment for DLTs will be performed after Day 28 of Cycle 1.

[b] EOT Visit will occur at the earliest day possible within 30 days after the last administration of milademetan or AZA (whichever is later). If the subject begins another form of anticancer therapy before the end of the 30-day period, every effort should be made to complete all 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] If the SCR Visit is performed within 24 hours of Cycle 1/Day 1, the assessments performed during SCR do not need to be repeated.

[e] AZA and milademetan administration will be done qd on Cycle 1/Days 6 to 7, and other assessments (except PK sampling) will be done on Day 7 pre-dose. If subjects receive AZA in the "5+2 schedule (Figure 3.3), all assessments, except PK sampling, will be done on Cycle 1/Day 8 instead of Day 7 and on Day 15 instead of Day 14, in these subjects.

[f] AZA administration will be done qd on Cycle 2/Days 1 to 4, and other assessments will be done on Day 1 pre-dose.

[g] AZA and milademetan administration will be done qd on Cycle 2/Days 5 to 7, and other assessments will be done on Day 7 pre-dose.
[h] Pregnancy test (serum) will be performed in female subjects of childbearing potential at SCR, Cycle 3/Day 1, and EOT Visit.
[i] Obtain a follicle stimulating hormone (FSH) test in women of childbearing potential to confirm menarche.
[j] At SCR, collect transfusion history for the 56 days prior to first dose of study drugs (first day exclusive).
[k] Vital sign measurements will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature.
[l] Safety laboratory samples for Day 1 pre-dose (hematology and serum chemistry) can be collected within 72 hours before the first dose. Creatinine clearance will be calculated at SCR.
[m] Electrocardiograms will be performed pre-dose unless specified, and at indicated post-dose time points on Cycle 1/Days 1, 5, and 14. Procedure window is ± 1 hour. When there is a PK sample collection corresponding to the time point for ECGs, the ECG should be performed within 10 minutes prior to PK sample collection. Other unscheduled ECGs may be performed as clinically indicated. Electrocardiograms will be performed in triplicate.
[n] For Cycle 1/Day 14, ECGs will be collected at the same time points as on Day 5. For subjects in Part 2 (Dose Expansion), ECGs are taken only at pre-dose and 3 hours post-dose on Day 5, and at pre-dose on Day 14 and other indicated visits.
[o] ECHO/MUGA do not need to be repeated if the procedure was done within 60 days before the first dose of study drugs and if no changes in cardiac conditions were observed based on the Investigator's clinical assessment.
[p] All unscheduled bone marrow assessments of disease burden performed on non-visit days must be reported as unscheduled visits. Bone marrow samples after the portion needed for disease assessment should be sent to the biomarker assessment per the Laboratory Manual instructions at SCR (Baseline), on Day 1 of Cycles 2 and 3 and then every 3 cycles thereafter (ie, at Day 1 of Cycles 6, 9, etc). Bone marrow re biopsy/aspirate after the EOT will also be sent for biomarker analysis.
[q] If bone marrow aplasia is observed on Cycle 2/Day1, study drug will be withheld and a confirmation bone marrow assessment will be performed in 2 weeks.
[r] Blood samples drawn pre-dose on Cycle 1/Days 1, 5, 7, and 14; Cycle 2/Days 1 and 15; Cycle 3/Day 1 and then every 3 cycles thereafter; and on EOT Visit will be sent for biomarker analysis per the Laboratory Manual.
[s] Milademetan is taken on Days 5 to 14 in each 28-day cycle.
[t] Blood samples for PK measurement will be collected pre-dose at the indicated visits, unless otherwise specified, and at indicated post-dose time points on Cycle 1/Days 5 and 14. Subjects will be instructed not to take their dose until after the sample has been collected on clinic days. Additional samples will be collected at the indicated time points. The PK time points and window for sample collection are specified in Table 8.1. Based on the PK profile established from the initial subjects treated in the study, sample collection time points may be modified upon notification by the Sponsor. If subjects receive AZA in the "5+2 schedule (Figure 3.3), the Cycle 1/Days 6, 7 and 14 PK samples are not collected.
[u] Six subjects in Part 1A will participate in an exploratory substudy. Blood samples will be collected at pre-dose and 0.5, 1, 2, 3, and 6 hours post-dose on Cycle 1/Day 1 (AZA alone) and Cycle 1/Day 7 (AZA + milademetan) (Table 8.3).
[v] On Cycle 1/Day 14, PK samples will be collected at the same time points as on Day 5 (Table 8.1). For subjects in Part 2 (Dose Expansion), sparse PK samples will be collected only on Cycle 1/Days 5 (0.5, 3, and 6 to 10 hours post-dose), 6 (pre-dose), and 14 (pre-dose and 3 to 6 hours post-dose) (Table 8.4). Cycle 1/Days 6, 7, and 14 PK sample will not be collected if subjects receive AZA in the "5+2" schedule (Figure 3.3).
[w] A blood sample will be collected for banking plasma on Cycle 1/Days 1 and 14, Cycle 2/Day 1, Cycle 3/Day 1, and then every 3 cycles thereafter (ie, Cycles 6, 9, 12, etc) corresponding to the timepoints for bone marrow biopsy/aspirate.
[x] 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.
[y] Serum for MIC-1 induction will be obtained at the indicated time points (pre-dose on Cycle 1/Day 1, pre-dose and at 6 to 10 hours post-dose on Cycle 1/Day 5, pre-dose on Cycle 1/Days 14 and 22, and pre-dose on Cycle 2/Day 15).
[z] A bone marrow re-biopsy or aspirate will be performed within 30 days of the last dose of study treatment, preferably prior to initiating new anticancer therapy, in subjects who have 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.
[aa] If feasible, collect subject survival status, date and cause of death (if applicable), subsequent anticancer therapy, and HCT and HCT-relevant information (if performed).

Table 17.3: Schedule of Events Part 1A (Dose Escalation) and Part 2 (Dose Expansion) – with Milademetan on Days 8 to 14 (Schedule F)

Cycle[a]	Pre-Cycle	1													2			3		4 +		Post-Cycle	
Visit Number	1	2		3-8	9							10	11	12-18		19	20-26		27 +			
Visit Description	SCR	EX		EX	EX						EX	EX	EX	EX		EX	EX		EX		EOT[b]	F/U[c]
Cycle Day(s)	-14 to 0	1[d]		2-7[e]	8						9	14[e]	22	1-6[f]	7[e]	15	1-6[f]	7[e]	1-6[f]	7[e]	ND	ND
Visit Window (days)												± 2	± 2	± 4			± 4		± 4		± 5	
Time post-dose (hours)		Pre-dose	2		Pre-dose	0 5	1	2	3	4	6-10												
Informed consent	X																					
Assign SID number	X																					
Demographics/medical history	X																					
Inclusion/exclusion criteria	X																					
Pregnancy test[g]	X																X				X	
Follicle stimulating hormone test[h]	X																					
Adverse events	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	
Record transfusion	X[i]	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	X	X			X								X	X		X	X		X		X	
Vital signs[j]	X	X	X	X	X							X	X	X	X	X	X	X	X	X	X	
Safety laboratory[k]	X	X			X								X	X	X	X	X	X	X		X	
ECG (12-lead)[l]	X	X	X		X[m]			X	X[m]	X	X	X	X[m]	X	X	X	X	X				X	
Echocardiogram/MUGA[n]	X																					
Bone marrow biopsy/aspirate[o]	X													X[p]		X[p]	X		X			
Buccal swab		X																				
Biomarker blood sample[q]		X			X							X		X		X	X		X		X	
AZA administration		X		X										X	X		X	X	X	X		
Milademetan administration[r]					X						X	X										
Blood sample for PK measurement[s]					X	X[t]	X	X	X[t]	X	X[t]	X[t]	X[t]	X								
Blood sample for banking plasma[u]		X										X		X		X			X			
MIC-1 serum sample[v]		X			X						X	X	X			X						
Dispense milademetan											X				X			X		X		
Pill diaries dispensed/reviewed					X						X	X			X	X		X		X	X	
Bone marrow re-biopsy/aspirate[w]																					X	
Record reason for discontinuation																					X	
Follow-up survival data[x]																					X	X

AZA = 5-azacitidine; CR = complete remission; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End-of-treatment; EX = exam; MIC-1 = macrophage inhibitory cytokine-1; MUGA = multigated acquisition; ND = not determined; PD = progressive disease; PK = pharmacokinetics; PR = partial remission; qd = once daily; SCR = Screening; SID = subject identification number; TBD = to be determined.

[a] Each cycle will last 28 days. Cohort safety assessment for DLTs will be performed after Day 28 of Cycle 1.

[b] EOT Visit will occur at the earliest day possible within 30 days after the last administration of milademetan or AZA (whichever is later). If the subject begins another form of anticancer therapy before the end of the 30-day period, every effort should be made to complete all 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] If the SCR Visit is performed within 24 hours of Cycle 1/Day 1, the assessments performed during SCR do not need to be repeated.

[e] AZA administration will be done qd on Days 3 to 7, and other assessments will be done on Day 7 pre-dose. If subjects receive AZA in the 5+2 schedule (Figure 3.3), the Cycle 1/Day 7 assessments will be moved to Day 8 and Day 14 assessments will be moved to Day 15, and no PK samples will be collected on these days.

[f] AZA administration will be done qd on Days 1 to 7, and other assessments will be done on Days 1 and 7 pre-dose.

[g] Pregnancy test (serum) will be performed in female subjects of childbearing potential at SCR, Cycle 3/Day 1, and EOT Visit.

[h] Obtain a follicle stimulating hormone (FSH) test in women of childbearing potential to confirm menarche.

[i] At SCR, collect transfusion history for the 56 days prior to first dose of study drugs (first day exclusive).

[j] Vital sign measurements will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature.

[k] Safety laboratory samples for Day 1 pre-dose (hematology and serum chemistry) can be collected within 72 hours before the first dose. Creatinine clearance will be calculated at SCR.

[l] Electrocardiograms will be performed pre-dose unless specified, and at indicated post-dose time points on Cycle 1/Days 1, 8, and 14. Procedure window is ± 1 hour. When there is a PK sample collection corresponding to the time points for ECGs, the ECG should be performed within 10 minutes prior to PK sample collection. Other unscheduled ECGs may be performed as clinically indicated. Electrocardiograms will be performed in triplicate.

[m] For Cycle 1/Day 14, ECGs will be collected at the same time points as on Day 8. For subjects in Part 2 (Dose Expansion), ECGs are taken only at pre-dose and 3 hours post-dose on Day 8, and at pre-dose on Day 14 and other indicated visits.

[n] ECHO/MUGA do not need to be repeated if the procedure was done within 60 days before the first dose of study drugs and if no changes in cardiac conditions were observed based on the Investigator's clinical assessment.

[o] All unscheduled bone marrow assessments of disease burden performed on non-visit days must be reported as unscheduled visits. Bone marrow samples after the portion needed for the disease assessment should be sent to the biomarker assessment per Laboratory Manual instructions at SCR (Baseline), on Day 1 of Cycles 2 and 3 and then every 3 cycles thereafter (ie, at Day 1 of Cycle 6, 9, etc). Bone marrow re biopsy/aspirate after the EOT will also be sent for biomarker analysis.

[p] If bone marrow aplasia is observed on Cycle 2/Day1, study drug will be withheld and a confirmation bone marrow assessment will be performed in 2 weeks.

[q] Blood samples drawn pre-dose Cycle 1/Days 1, 8, and 14; Cycle 2/Days 1 and 15; Cycle 3/Day 1 and then every 3 cycles thereafter; and on EOT Visit will be sent for biomarker analysis per the Laboratory Manual.

[r] Milademetan is taken on Days 8 to 14 in each 28-day cycle.

[s] Blood samples for PK measurement will be collected pre-dose at the indicated visits, unless otherwise specified, and at indicated post-dose time points on Cycle 1/Days 8 and 14. Subjects will be instructed not to take their dose until after sample has been collected on clinic days. Additional samples will be collected at the indicated time points and as clinically indicated. The PK time points and window for sample collection are specified in Table 8.2. Based on the PK profile established from the initial subjects treated in the study, sample collection time points may be modified upon notification by the Sponsor.

[t] On Cycle 1/Day 14, PK samples will be collected at the same time points as on Day 8 (Table 8.2). For subjects in Part 2 (Dose Expansion), sparse PK samples will be collected only on Cycle 1/Days 8 (0.5, 3, and 6 to 10 hours post-dose), 9 (pre-dose), and 14 (pre-dose and 3 to 6 hours post-dose) (Table 8.4). PK samples, for Cycle 1 Day 6 and Day 14 will not be collected for subjects on the alternative (5+2) AZA schedule (Figure 3.3).

[u] A blood sample will be collected for banking plasma on Cycle 1/Days 1 and 14, Cycle 2/Day 1, Cycle 3/Day 1, and then every 3 cycles thereafter (ie, Cycles 6, 9, 12, etc) corresponding to the timepoints for bone marrow biopsy/aspirate.

[v] Serum for MIC-1 induction will be obtained at the indicated time points (pre-dose on Cycle 1/Day 1, pre-dose and at 6 to 10 hours post-dose on Cycle 1/Day 8, pre-dose on Cycle 1/Days 14 and 22, and pre-dose on Cycle 2/Day 15).

[w] A bone marrow re-biopsy or aspirate will be performed within 30 days of the last dose of study treatment, preferably prior to initiating new anticancer therapy, in subjects who have 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.

[x] If feasible, collect subject survival status, date and cause of death (if applicable), subsequent anticancer therapy, and HCT and HCT-relevant information (if performed).

17.2. Eastern Cooperative Oncology Group Performance Status Scale[14]

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

17.3. National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (Version 4.03 before 01 Apr 2018)

1. Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.
2. When 2 different criteria grades might be applicable for rating a particular toxicity, or similar toxicities, the more severe grade should be used.
3. Any toxicity resulting in death is defined as Grade 5.
4. The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.
5. For links to the National Cancer Institute Common Terminology Criteria for Adverse Events refer to:
   - Version 4.03:

     https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40
   - Version 5.0:

     https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50

17.4. Response Criteria for AML

17.4.1. 2017 European LeukemiaNet Recommendations for Acute Myelogenous Leukemia with Modifications (Part 2 Only)[16]

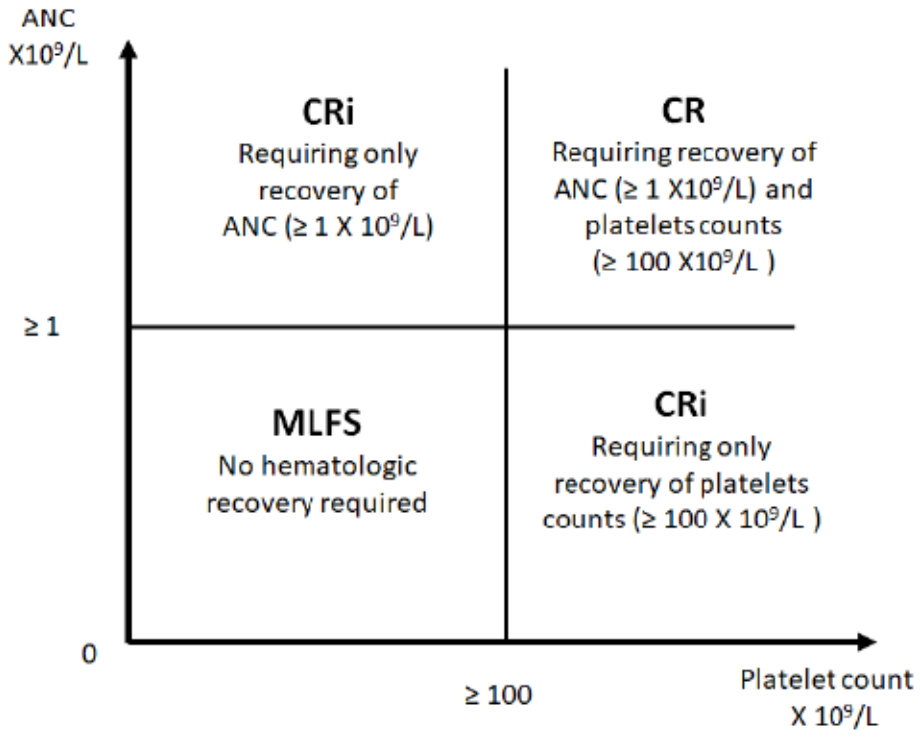
Category	Definition
Complete Remission (CR)	• Bone marrow blasts <5% • Absence of circulating blasts and blasts with Auer rods • Absence of extramedullary disease • Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L • Platelet count $\geq 100 \times 10^9$/L
CR with Incomplete Blood Count Recovery (CRi) (Figure 17.1)	All CR criteria except for residual neutropenia (ANC $<1.0 \times 10^9$/L) or thrombocytopenia (platelet count $<100 \times 10^9$/L)
Morphologic Leukemia-free State (MLFS)	• Bone marrow blasts <5% • Absence of blasts with Auer rods • Absence of extramedullary disease • No hematologic recovery required o **Note**: Marrow should not merely be "aplastic"; at least 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: o ANC $\geq 1.0 \times 10^9$/L o platelet count $\geq 100 \times 10^9$/L
Stable Disease (SD)	Absence of CR, CRi, MLFS, or PR, and criteria for PD not met o **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 ≥5%, or • 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 extramedullary disease

ANC = absolute neutrophil count; WBC = white blood cells

17.4.2. Hematologic Recovery Requirements for CR and CRi (All Parts)

Figure 17.1: Hematologic Recovery Requirements for CR and CRi (All Parts)



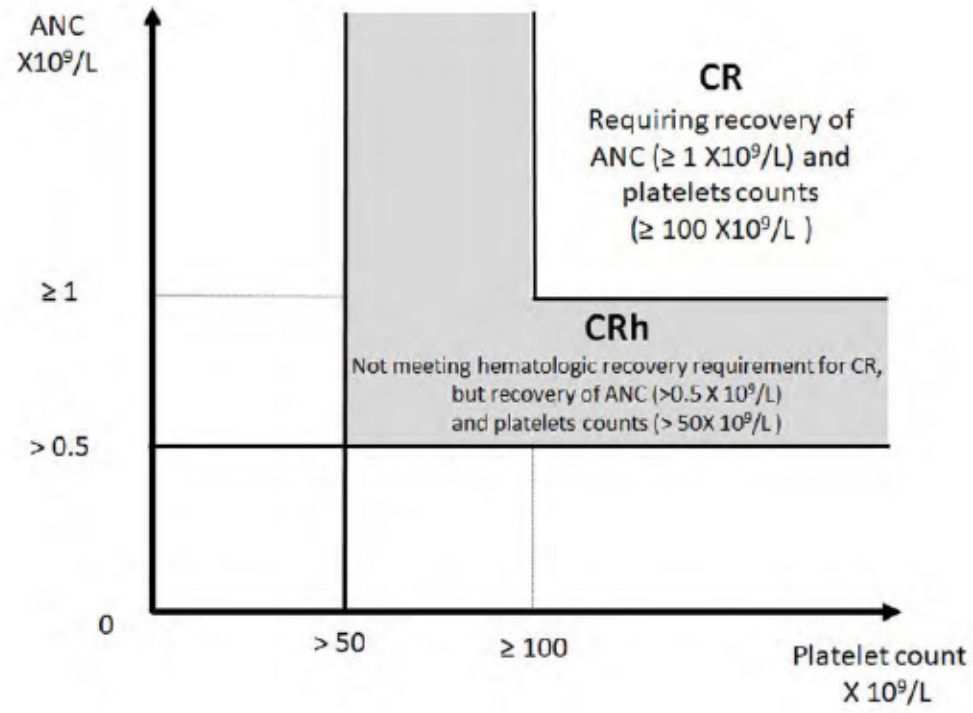
ANC = absolute neutrophil count; CR = complete remission; CRi = CR with incomplete blood count recovery; MLFS = morphologic leukemia-free state

17.4.3. CRh (Additional Definitions/Response Criteria) (All Parts)[17]

CRh evaluation will be conducted separately from those in Section 17.4.1.

Category	Definition
CR with Partial Hematological Recovery (CRh) (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 (All Parts)



ANC = absolute neutrophil count; CR = complete remission; CRh = CR with partial hematological recovery

17.4.4. 2003 International Working Group Response Criteria for Acute Myelogenous Leukemia with Modifications (Part 1 and Part 1A Only)[15]

Category	Definition
Complete Remission (CR)	• Bone marrow blasts <5% • Absence of circulating blasts and blasts with Auer rods • Absence of extramedullary disease • ANC ≥1.0 × 10^9/L and platelet count ≥100 × 10^9/L
CR with Incomplete Blood Count Recovery (CRi)	• All CR criteria except for ANC <1.0 × 10^9/L OR platelet count <100 × 10^9/L
Partial Remission (PR)	• Decrease of bone marrow blast percentage by at least 50% to a value of 5% to 25% and ANC ≥1.0 × 10^9/L; 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
Treatment Failure	• Persistent AML in blood or bone marrow, or therapy fails to achieve a remission of any category, or death prior to response assessment

AML = acute myelogenous leukemia; ANC = absolute neutrophil count

17.5. Response Criteria for MDS

17.5.1. 2006 International Working Group Response Criteria for Myelodysplastic Syndrome[16]

Table 17.4: Response Criteria

Category	Response Criteria[a]

Complete Remission (CR)	• Bone marrow: ≤5% myeloblasts with normal maturation of all cell lines[b]
	• Persistent dysplasia will be noted[b]
	• Peripheral blood
	  ○ Hgb ≥11 g/dL
	  ○ Platelets ≥100 × 10^9/L
	  ○ Neutrophils ≥1.0 × 10^9/L
	  ○ Blasts 0%

Marrow CR (mCR)	• Bone marrow: ≤5% myeloblasts and decrease by ≥50% over pretreatment • Peripheral blood: If hematologic improvement responses, they will be noted in addition to mCR

Partial Remission (PR)	• All CR criteria if abnormal before treatment except:
	  ○ Bone marrow blasts decreased by ≥50% over pretreatment but still >5%
	  ○ Cellularity and morphology not relevant

Cytogenetic Response	• Complete:
	  ○ Disappearance of the chromosomal abnormality without appearance of new ones
	• Partial:
	  ○ At least 50% reduction of the chromosomal abnormality

Stable Disease (SD)	• Failure to achieve at least PR, but no evidence of progression for >8 weeks **Note**: SD can be reported as each assessment not persisting for 8 weeks, whereas SD which persists for at least 8 weeks will be summarized for the efficacy analysis

Relapse after CR or PR	• At least 1 of the following:
	  ○ Return to pretreatment bone marrow blast percentage
	  ○ Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets
	  ○ Reduction in Hgb concentration by ≥1.5 g/dL or transfusion dependence

Category	Response Criteria[a]
Disease Progression	• For subjects with: o Less than 5% blasts: ≥50% increase in blasts to >5% blasts o 5% to 10% blasts: ≥50% increase to >10% blasts o 10% to 20% blasts: ≥50% increase to >20% blasts o 20% to 30% blasts: ≥50% increase to >30% blasts Any of the following: o ≥50% decrement from maximum remission/response in granulocytes or platelets o Reduction in Hgb by ≥2 g/dL o Transfusion dependence

Hgb = hemoglobin

[a] Study sites can report CR, mCR, PR or cytogenetic response at each assessment even when response does not persist for 4 weeks. However, CR, PR, mCR or cytogenetic response which persists for at least 4 weeks will be summarized for the efficacy analysis.

[b] Dysplastic changes should consider the normal range of dysplastic changes.

Table 17.5: Hematologic Improvement

Category	Response Criteria[a,b]
Erythroid response based on Hgb increase (pretreatment, <11 g/dL)[c]	• Hgb increase by ≥1.5 g/dL
Erythroid response based on reduction of RBC transfusion	• Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hgb of ≤9.0 g/dL pretreatment will count in the RBC transfusion response evaluation.
Platelet response (pretreatment, $<100 \times 10^9$/L)[c]	• Absolute increase of $\geq 30 \times 10^9$/L for subjects starting with $>20 \times 10^9$/L platelets • Increase from $<20 \times 10^9$/L to $>20 \times 10^9$/L and by at least 100%
Neutrophil response (pretreatment, $<1.0 \times 10^9$/L)[c]	• At least 100% increase and an absolute increase $>0.5 \times 10^9$/L
Progression or relapse after hematologic improvement[d]	• At least 1 of the following: o ≥50% decrement from maximum response levels in granulocytes or platelets o Reduction in Hgb by ≥1.5 g/dL o Transfusion dependence

Hgb = hemoglobin; RBC = red blood cell

[a] Responses must last at least 8 weeks.

[b] Study sites can report erythroid, platelet, or neutrophil response at each assessment even when response does not persist for 8 weeks. However, erythroid, platelet, or neutrophil response which persists for at least 8 weeks will be summarized for the efficacy analysis.

[c] Pretreatment counts averages of at least 2 measurements ≥1 week apart (not influenced by transfusions, ie, no RBC transfusions for at least 1 week and no platelet transfusions for at least 3 days).

[d] In the absence of another explanation, such as acute infection, repeated courses of chemotherapy, gastrointestinal bleeding, hemolysis, and so forth. It is recommended that the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

17.6. Revised International Prognostic Scoring System[19]

Table 17.6: The International Prognostic Scoring System – Revised Parameters and Score Values

Prognostic Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor
BM Blast %	≤2		>2 to <5%		5 to 10%	>10%	
Hemoglobin	≥10		8 to <10	<8			
Platelets	≥100	50 to <100	<50				
ANC	≥0.8	<0.8					

ANC = absolute neutrophil count; BM = bone marrow

Table 17.7: The International Prognostic Scoring System – Revised Risk Groups

Risk Group	Risk Score
Very Low	≤1.5
Low	>1.5 to 3
Intermediate	>3 to 4.5
High	>4.5 to 6
Very High	>6

17.7. Cytochrome P450 3A Inducers and Inhibitors

The following list describes medications that are strong inhibitors of CYP3A that need milademetan dose adjustment if used concomitantly, and inducers of CYP3A that are prohibited during treatment with azacitidine and milademetan combination. This list should not be considered all-inclusive.

Strong CYP3A Inhibitors	**Strong CYP3A Inducers**
Boceprevir	Avasimibe
Clarithromycin	Carbamazepine
Conivaptan	Phenytoin
Grapefruit	Rifampin
Grapefruit juice	St. John's Wort
Indinavir	
Itraconazole	
Ketoconazole	
Lopinavir	
Mibefradil	
Nefazodone	
Nelfinavir	
Posaconazole	
Ritonavir	
Saquinavir	
Telaprevir	
Telithromycin	
Voriconazole	

http://medicine.iupui.edu/clinpharm/ddis/table.aspx

17.8. New York Heart Association (NYHA) Functional Classifications

The following table lists the NYHA Classes of Heart Failure.[20]

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.

17.9. Highly Effective Methods of Birth Control

Per the guidance from the Clinical Trial Facilitation Group (CTFG) of the European Heads of Medicines Agencies (HMA),[21] 66 methods that can achieve a failure rate of less than 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 study drugs, the Investigator will discuss highly effective methods of birth control as defined above with women of childbearing potential (as defined in Section 4.1.1) and men who are not surgically sterile.