CLINICAL STUDY PROTOCOL

PHASE 1, OPEN-LABEL, DOSE ESCALATION STUDY OF DS-3032B, AN ORAL MDM2 INHIBITOR, TO ASSESS SAFETY, TOLERABILITY AND PHARMACOKINETICS IN JAPANESE PATIENTS WITH RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA

DS3032-A-J104

VERSION 01.4, 07 OCT 2019

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PROTOCOL SYNOPSIS

Protocol Number:	DS3032-A-J104
Investigational Substance Code:	DS-3032b
Generic Name/INN:	milademetan
Study Title:	Phase 1, open-label, dose escalation study of DS-3032b, an oral MDM2 inhibitor, to assess safety, tolerability and pharmacokinetics in Japanese patients with relapsed or refractory acute myeloid leukemia
Study Phase:	Phase 1
Indication Under Investigation:	Acute myeloid leukemia (AML)
Study Objectives:	Primary objective: To evaluate the safety and tolerability of DS-3032b monotherapy administered as multiple doses and assess the maximum tolerated dose (MTD) in Japanese subjects with relapsed or refractory AML. Secondary objectives: • To evaluate the pharmacokinetics of DS-3032a • To exploratively evaluate the antitumor effect of DS-3032b Type of study objectives: Efficacy, safety, pharmacodynamics, pharmacokinetics, tolerability, pharmacogenomics
Study Design:	Type of study: Interventional Type of intervention: Pharmaceutical drugs Type of proposed indications: Treatment Study design: Single arm Dose finding method: An optimal dose of DS-3032b will be explored from among four doses (Subtrials A, B, C, and D) based on the fixed dosing schedule. The study will be started from Subtrial A, and other subtrials will be conducted as necessary. Explorative assessment of MTD in each subtrial will be guided by a modified continual reassessment method (mCRM) using a Bayesian logistic regression model (BLRM) incorporating the escalation with overdose control (EWOC) principle.

Combinations of Doses and Dosing Schedules

Dose (mg)	Subtrial C	Subtrial B	Subtrial A	Subtrial D
160	C-3	B-3	A-3	D-3
120	C-2	B-2	A-2	D-2
90	C-1	B-1	A-1	D-1
	3/14 × 2	7/28	14/28	21/28

Dosing schedule (day/day)

Level of blinding: Open-label
Type and presence/absence of comparator: Not applicable
Add-on to standard therapy: None

Study Duration:	06 Jul 2018 to 31 Dec 2019
Location:	Japan
Study Centers:	Refer to Attachment 2.
Planned Sample Size:	9 to 24 subjects
Study Population (Inclusion and Exclusion Criteria)	Inclusion criteria 1. Provision of written informed consent for participation in this study. 2. Age ≥20 years old upon enrollment in this study. 3. Having AML (including those with a history of myelodysplastic syndrome [MDS]) satisfying either of the following: • Have failed to achieve remission with at least 1 cycle of prior induction therapy • Have relapsed after achieving remission with prior therapy 4. Those who appear unable to achieve persistent remission with standard treatment, who failed to complete potentially curative treatment, or who have no treatment options with expected therapeutic efficacy. 5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2 (refer to "Appendix 2"). 6. Having laboratory data satisfying all of the following criteria in the measurement within 14 days before enrollment in this study.

Laboratory Parameter	Requirement
AST	≤2.5 × the upper limit of normal of the center (ULN)
ALT	≤2.5 × ULN
Total bilirubin	≤1.5 × ULN
Serum creatinine	Creatinine clearance ≥60 mL/min, as calculated using the modified Cockcroft Gault equation*
	In case of creatinine clearance ≥50 mL/min and <60 mL/min, as calculated using the above equation, the subject may be enrolled if the serum creatinine level is ≤1.5 × ULN.
Prothrombin time-international normalized ratio (PT-INR)	≤1.5 × ULN
Activated partial thromboplastin time (aPTT)	≤1.5 × ULN

*: ([140 − age (year)] × [actual weight (kg)]) / [72 × serum creatinine (mg/dL)] (× 0.85 [if female])

7. Able to take the following interval during the period from the last dose or last procedure of prior therapy to the start day of treatment with the study drug (study treatment) in this study.
   - Cytotoxic drugs: 2 weeks (48 hours for hydroxycarbamide used for the purpose of controlling the increase in white blood cells)
   - Non-cytotoxic drugs: At least 5 times the half-life of the drug
8. Women of childbearing potential must have a negative pregnancy test at screening and must be willing to use highly effective birth control (eg, barrier contraceptives with spermicides, intrauterine device) during the following period: Upon enrollment, during the treatment period, and for at least 95 days after the last dose of DS-3032b.

   Women of childbearing potential are those in the period from first menstruation to menopause (no menstrual period for a minimum of 12 months). This, however, shall exclude permanently (surgically) sterile women.
9. Males must be surgically sterile or willing to use highly effective birth control upon enrollment, during the treatment period, and for at least 95 days after the last dose of DS-3032b. Male subjects may not donate their sperm during the study period and for at least 95 days after the last dose of DS-3032b.
10. Able to be hospitalized during the dose-limiting toxicity (DLT) evaluation period.

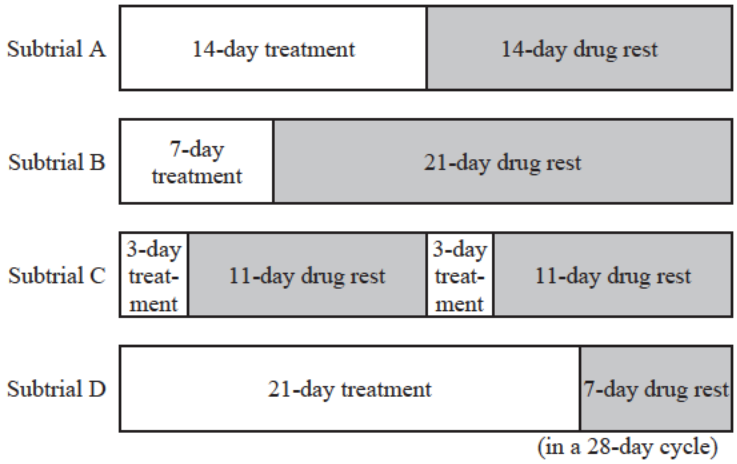
Study Population (Inclusion and Exclusion Criteria)	Exclusion criteria 1. Diagnosis of acute promyelocytic leukemia. 2. Chronic myeloid leukemia in blast crisis (positive for a breakpoint cluster region- c-Abelson [BCR-ABL] fusion gene). 3. History of or concurrent central nervous system leukemia. 4. History of hematopoietic stem cell transplant (HSCT) and meeting any of the following: • Transplantation within 60 days before the start of study treatment • Persistent graft-versus-host disease (GVHD) that is clinically significant, requires the start of treatment, or requires intensification of treatment within 21 days before informed consent • Persistent Grade ≥2 clinically significant or irreversible non-hematological toxicity related to transplantation 5. Uncontrolled infection requiring intravenous antibiotics, antifungals, or antivirals. 6. A positive test result for hepatitis C virus (HCV) antibody or human immunodeficiency virus (HIV) antibody within 90 days before enrollment. 7. A positive test result for hepatitis B surface (HBs) antigen within 90 days before enrollment. 8. A positive test result for hepatitis B core (HBc) antibody or HBs antibody with hepatitis B virus (HBV)-DNA levels ≥2.1 log copies/mL, despite a negative test result for HBs antigen, within 90 days before enrollment. 9. Receiving strong cytochrome P450 (CYP) 3A inhibitors within 7 days before the start of study treatment. 10. Receiving strong CYP3A inducers within 14 days before the start of study treatment. 11. History of or current cardiovascular disease as specified below: • QT corrected for heart rate using Fridericia's method (QTcF) interval >450 ms, determined as the average of triplicate electrocardiogram (ECG) measurements taken within 14 days before enrollment in this study • Class III or more severe congestive heart failure according to "Appendix 3 New York Heart Association (NYHA) Functional Classification" within 6 months before enrollment in this study • History of myocardial infarction within 6 months before enrollment in this study • History of angina pectoris attack within 6 months before enrollment in this study

- History of arrhythmia requiring treatment within 6 months before enrollment in this study
- Need for a pacemaker or implantable cardioverter defibrillator
- Diagnosed or suspected congenital long QT syndrome
- History of life-threatening ventricular arrhythmia (ventricular tachycardia, ventricular fibrillation, or torsades de pointes)
- History of bradyarrhythmia (eg, atrioventricular block)
- Clinically significant electrolyte abnormalities that can induce secondary long QT syndrome
- Uncontrolled hypertension despite pharmacotherapy etc.

12. Adverse drug reactions (excluding alopecia) to previous therapy (treatment for AML and/or anticancer therapy), which have not resolved or returned to Grade 1 or baseline. Patients with chronic Grade 2 adverse drug reactions (eg, chemotherapy-induced neuropathy) may be eligible when the investigator or subinvestigator decides that there are no clinical safety concerns from the standpoint of the patient's safety.

    * The grade will be assessed according to the "Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0."

13. History of another malignant tumor requiring treatment within 2 years before enrollment in this study. However, patients whose disease is considered to have been cured by local treatment (eg, non-melanoma skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast) may be eligible for participation in the study.
14. Predisposition to serious infection (eg, cystic fibrosis, congenital or acquired immunologic disease, hemorrhagic disease, or cytopenia unrelated to AML).
15. Disseminated intravascular coagulation or other clinically significant coagulation abnormalities.
16. Extensive surgery within 28 days before the start of study treatment.
17. Radiation therapy within 28 days before the start of study treatment.
18. Any factor that could preclude adequate absorption of DS-3032b (eg, refractory nausea and vomiting, malabsorption, biliary shunt, significant bowel resection, and/or GVHD affecting the gut).
19. Pregnant or breastfeeding women.
20. Patients who are otherwise considered ineligible for the study in the opinion of the investigator or subinvestigator.

Study Drug(s):	Dose: The starting dose of DS-3032b in Subtrial A will be 90 mg. The subsequent doses will be determined, taking the following into consideration. i) Recommended dose, guided by mCRM using a BLRM incorporating the EWOC principle ii) Clinical evaluation of the toxicological profile and information on pharmacokinetics/pharmacodynamics (PK/PDy) Dose increments should be at least 1.3-fold in order to make a distinction among the dose cohorts, considering inter-subject variability in exposure. Even if the recommended dose for the next cohort calculated by the model is more than 2-fold, the dose should be no more than 2-fold. Regimen: In Subtrial A, the study drug will be administered on Days 1 to 14, followed by a 14-day rest, in a 28-day cycle (14/28 schedule). Each cycle is 28 days long. The study treatment will be continued in 28-day cycles until any of the withdrawal criteria apply. Assessment of the other dosing schedules (Subtrials B, C, and D) will be conducted if it becomes necessary to evaluate the safety of DS-3032b. Dosing schedules in each subtrial are shown in the table below.  Capsules with two different strengths will be used as the study drug (30 mg and 100 mg). The study drug will be orally taken once daily (qd). Meal consumption should be avoided from 2 hours before dosing to 1 hour after dosing.
Prohibited concomitant drugs and therapies, and restricted concomitant drugs:	Prohibited concomitant drugs and therapies: • From informed consent to the day of the Follow-up: Anticancer treatment other than the study drug (excluding hydroxycarbamide), other investigational products, and investigational medical devices

	• From 14 days before the start of study treatment to the day of the Follow-up: Strong CYP3A inducers and St. John's wort-containing foods and supplements • From 7 days before the start of study treatment to the day of the Follow-up: Strong CYP3A inhibitors and grapefruit-containing foods and beverages Restricted concomitant drugs: • Hydroxycarbamide should be used as per the following instructions. Use of hydroxycarbamide is prohibited during the period from 48 hours before treatment with DS-3032b to the start of treatment with DS-3032b. It is, however, allowed to concomitantly use hydroxycarbamide to control white blood cell counts at doses up to 5 g/day for a total of 8 days or less only during the period from after the start of treatment with DS-3032b to the end of the Follow-up. • Prophylactic treatment for the following symptom is prohibited during the DLT evaluation period. However, treatment given as supportive care for the following symptom is allowed. Neutropenia: Granulocyte colony stimulating factor (G-CSF) products etc.
Study procedures:	Refer to Appendix 1.
Study Endpoints:	Safety endpoints: Adverse events (AE), ECOG PS, laboratory data, body weight, vital signs, and 12-lead ECG Efficacy endpoints: Complete remission (CR), CR with incomplete hematological recovery (CRi), CR with partial hematological recovery (CRh), partial remission (PR), morphologic leukemia-free state (MLFS), stable disease (SD), progressive disease (PD), composite CR (CRc) rate (CR + CRi + CRh), response rate (CRc + PR), and duration of CRc Pharmacokinetic endpoints: Plasma DS-3032a concentration and pharmacokinetic parameters (Subtrial A) C1D1 (Cycle 1 Day 1): Cmax, Tmax, AUClast, AUC8h, AUC24h, AUCinf*, Kel*, t1/2*, CL/F*, Vz/F* C1D14 (Cycle 1 Day 14)**: Cmax, Ctrough, Cavg, Tmax, AUC8h, AUC24h, Kel*, t1/2*, CLss/F***, Vz/F*.***, AR

	*: To be calculated only if possible. **: To be read as C1D7 (Cycle 1 Day 7) in Subtrial B, C1D3 (Cycle 1 Day 3) in Subtrial C, and C1D15 (Day 15) in Subtrial D. ***: Not to be calculated because steady state will not be reached in Subtrial C. Pharmacodynamic endpoints: Tumor protein p53 gene (*TP53*) mutation and serum macrophage inhibitory cytokine-1 (MIC-1) level
Primary statistical analyses:	Safety analyses: The DLT rate will be estimated for each dose using mCRM based on DLT evaluation data of all evaluable subjects, and the MTD will then be determined. AEs that occur or worsen after the start of study treatment will be summarized in frequency tables by event, causality with the study drug, and grade according to the CTCAE. For laboratory data, vital signs, body weight, and 12-lead ECGs, a frequency table or shift table will be prepared for categorical data and summary statistics will be calculated for quantitative data. Also, frequency table(s) with detailed descriptions of DLTs (if any) will be prepared. Efficacy analyses: Frequency tables will be prepared for best response. The CRc rate, response rate, and transplantation rate will be calculated. Summary statistics will be calculated for the duration of CRc. Pharmacokinetic analyses: Pharmacokinetics will be analyzed for each subtrial. Summary statistics of plasma concentrations of DS-3032a will be calculated by dose at each time point, and a plasma concentration-time profile will be prepared. For the pharmacokinetic parameters that are calculated by the non-compartmental analysis, summary statistics will be calculated by dose. Pharmacodynamic analyses: For PDy values and PDy parameters, summary statistics will be calculated by treatment group. Adaptive design: Present
Withdrawal Criteria of the Study:	Subjects will be withdrawn from the study for the following reasons. 1. Apparent progression of the disease is found. 2. It becomes difficult to continue the study treatment due to

AEs (refer to "Section 5.5 Actions to be Taken for Adverse Events").

3. A *TP53* mutation is detected after study treatment and it is decided inappropriate to continue the study for the subject.
4. The subject is found to be ineligible for the study after enrollment in the study.
5. The subject withdraws his/her consent to participation in the study.
6. The sponsor decides to prematurely terminate the study.
7. The subject has received the study drug on less than 75% of the specified number of dosing days in Cycle 1.
8. Other cases that the investigator or subinvestigator judges it inappropriate to continue the study for the subject.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ALL	acute lymphocytic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BCR-ABL	breakpoint cluster region- c-Abelson
BLRM	Bayesian logistic regression model
BUN	blood urea nitrogen
CFU-GM	colony forming unit-granulocyte/macrophage
CHL	Chinese hamster lung
CML	chronic myelogenous leukemia
CR	complete remission
CRc	composite CR
CRh	CR with partial hematological recovery
CRi	CR with incomplete hematological recovery
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capturing
EWOC	escalation with overdose control
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GI_{50}	concentration causing 50% growth inhibition
GVHD	graft-versus-host disease

ABBREVIATION	DEFINITION
HBc	hepatitis B core
HBs	hepatitis B surface
HBV	hepatitis B virus
HCV	hepatitis C virus
hERG	human ether-a-go-go related gene
HIV	human immunodeficiency virus
HNSTD	highest nonseverely toxic dose
HSCT	hematopoietic stem cell transplantation
IC_a (IC_{50}, IC_{75}, IC_{90})	concentration causing a% inhibition
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRB	Institutional Review Board
mCRM	modified continual reassessment method
MDM2	murine double minute 2
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MIC-1	macrophage inhibitory cytokine-1
MLFS	morphologic leukemia-free state
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
NOAEL	no observed adverse effect level
NRU	neutral red uptake
NYHA	New York Heart Association
PD	progressive disease
PDy	pharmacodynamic(s)
PGx	pharmacogenomic(s)
PIF	photo irritation factor
PK	pharmacokinetic(s)
PR	partial remission
PS	performance status
PT	preferred term
PT-INR	prothrombin time-international normalized ratio

ABBREVIATION	DEFINITION
qd	once daily
QT	interval between the start of the Q wave and the end of the T wave
QTcB	QT corrected for heart rate using Bazett's formula
QTcF	QT corrected for heart rate using Fridericia's method
RP2D	recommended phase 2 dose
SAVER	serious adverse event report
SD	stable disease
SOC	system organ class
STD_{10}	severely toxic dose in 10% of the animals
TEAE	treatment emergent adverse event
TP53	tumor protein p53 gene
WHO	World Health Organization

LIST OF PHARMACOKINETIC PARAMETERS

ABBREVIATION	DEFINITION
AR	observed accumulation ratio
AUC	area under the plasma concentration-time curve
AUC8h	area under the plasma concentration-time curve during 8 hours
AUC24h	area under the plasma concentration-time curve during 24 hours
AUCinf	area under the plasma concentration-time curve up to infinity
AUClast	area under the plasma concentration-time curve up to the last quantifiable time
Cavg	average plasma concentration
Cmax	maximum plasma concentration
Ctrough	trough plasma concentration
CL/F	apparent total body clearance
CLss/F	apparent total body clearance at steady state
Kel	apparent terminal elimination rate constant
t1/2	terminal elimination half-life
Tmax	time to reach maximum plasma concentration
Vz/F	apparent volume of distribution based on the terminal phase

LIST OF TERMS

TERMS	DEFINITION
DS-3032b	Development code of milademetan
DS-3032a	Free form of DS-3032b
DOHH-2	B-cell lymphoma cell line
MOLM-13	Human acute myeloid leukemia cell line
RG7112	MDM2 antagonist
RG7388	MDM2 antagonist
SAR405838	MDM2 antagonist
SJSA-1	Osteosarcoma cell line
WM-115	Melanoma cell line

1. INTRODUCTION

1.1. Background of This Study

Acute myeloid leukemia (AML) is a hematological malignant tumor characterized by autonomous growth of myeloid blast cells (myeloblasts) that are unable to differentiate or further develop into mature white blood cells, and its clinical presentation is diverse.[1] According to "Cancer Registration and Statistics" of the Cancer Information Service, National Cancer Center, the crude prevalence rate of leukemia is 9.6 (11.4 for males and 7.9 for females) per 100,000 people in 2011 and it is increasing each year.[2] The prevalence rate of AML by itself is unknown; however, acute leukemia accounts for about 80% of all leukemias, and AML accounts for approximately 80% of adult acute leukemia cases and 20% of pediatric acute leukemia cases.[3] While AML has become a disease that is considered curable in recent years, the long-term survival rate after complete remission (CR) with chemotherapy in AML patients remains low at about 40%.[4] At present, there are no molecular targeting drugs that can be used for newly diagnosed AML patients, and the relapse rate still remains high. In Japan, relapsed or refractory AML patients are treated with monotherapy or combination therapy with cytarabine, mitoxantrone, etoposide, fludarabine, aclarubicin, gemtuzumab ozogamicin, and others. None of these therapies, however, provide an adequate therapeutic effect, or no standard treatment has been established for these patients.[5] Accordingly, how to prevent relapse is a major concern for chemotherapy.

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. The activity of p53 can be lost due to its mutations or defects but is frequently inhibited by intermolecular interactions between p53 and murine double minute 2 (MDM2) in human tumors harboring wild-type p53. In normal cells, p53 is controlled by MDM2. MDM2 promotes p53 nuclear export or degradation of p53 through the ubiquitin proteasome pathway, and thereby maintains low levels of p53 activity.[6] It has also been reported that p53 becomes activated in the presence of stress, and subsequently acts as a transcription factor that modulates the expression of a variety of genes, including MDM2.[7]

In humans, the balance between MDM2 and p53 is disrupted by overexpression and/or oncogenic activation of MDM2, which reduces p53 function, potentially allowing tumorigenesis and tumor growth. Pharmacologic inhibition of the interaction between MDM2 and p53 in tumor cells harboring wild-type p53 could therefore result in a sustained increase in p53 activity and subsequent antitumor effects.[8,9] Therefore, MDM2 is considered to become a treatment target for various forms of malignant tumors.[10] Approximately 90% of AML patients retain wild-type tumor protein p53 gene (*TP53*) in their leukemia cells, in which p53 activity is maintained at a low level by binding of overexpressed MDM2.[11]

DS-3032b is a small-molecule inhibitor of MDM2 that 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 by Daiichi Sankyo Co., Ltd.

In vitro studies demonstrated that DS-3032b inhibits the MDM2-p53 interaction and induces p53 target gene expression. In the study of DS-3032b for tumor growth inhibition in 6 human cancer cell lines with different p53 status, DS-3032b exhibited p53 status-dependent antitumor effects. DS-3032b demonstrated more potent antitumor effects in the p53 wild-type cell line than the positive control Nutlin-3a, known as a small-molecule MDM2 inhibitor. In in vivo studies in male nude mice subcutaneously inoculated with SJSA-1 human osteosarcoma cell line, orally given DS-3032b exhibited dose-dependent antitumor effects. In a study that evaluated the antitumor effects of DS-3032b in combination with either quizartinib or 5-azacytidine in male mice subcutaneously inoculated with human acute myeloid leukemia cell line (MOLM-13), DS-3032b exhibited antitumor effects when used as a single agent or in combination with quizartinib or 5-azacytidine.

Based on the above results, DS-3032b is considered to have the potential to become a new drug for the treatment of hematological cancers including AML, and a clinical study was planned. A Phase 1 study of DS-3032b in subjects with advanced hematological cancers including AML is currently underway in the US. To date, decreases in myeloblasts and CR have been achieved in several subjects treated with DS-3032b monotherapy in the study.

Accordingly, it was decided to start clinical development of DS-3032b in Japan, and this study was planned to evaluate the safety and pharmacokinetics of DS-3032b monotherapy in subjects with relapsed or refractory AML.

1.2. Summary of Significant Findings Obtained from Nonclinical Studies

1.2.1. Pharmacology

In vitro studies demonstrated that DS-3032b inhibits the MDM2-p53 interaction and induces p53-dependent gene expression. In the study that evaluated potential tumor growth inhibition of DS-3032b in 6 human cancer cell lines with different p53 status, DS-3032b exhibited superior growth inhibitory effects in the human p53 wild-type acute leukemia cell line (MOLM-13), B-cell lymphoma cell line (DOHH-2), osteosarcoma cell line (SJSA-1), and melanoma cell line (WM-115) at lower doses, compared with Nutlin-3a. On the other hand, no growth inhibition of DS-3032b was observed in the p53 mutant or null cell line. These results demonstrated that DS-3032b exhibits antitumor effects p53 status-dependently and exerts more potent antitumor effects than Nutlin-3a in cancer cells harboring wild-type p53.

In vivo studies in male nude mice subcutaneously inoculated with SJSA-1 human osteosarcoma cell line demonstrated that DS-3032b exhibits dose-dependent antitumor effects. In the study that evaluated schedule-dependent effects (3 dosing schedules of DS-3032b at a total of 250 mg/kg [25 mg/kg once daily for 10 days [qd × 10], 62.5 mg/kg every 3 days, 4 times in 12 days [q3d × 4], or 125 mg/kg every 7 days, twice in 2 weeks [q7d × 2]), DS-3032b exhibited antitumor effects with all the dosing schedules, with no difference in the antitumor effects among the dosing schedules.

Furthermore, DS-3032b was assessed for potential in vivo antitumor effects when used in combination with either quizartinib or 5-azacytidine in male mice subcutaneously inoculated with MOLM-13. In the assessment of the combination of DS-3032b and quizartinib both given orally once daily for 11 days (qd × 11), tumor growth inhibition of DS-3032b as a single agent was 27.3% and 60.5% in the 25 mg/kg/dose and 50 mg/kg/dose groups, respectively. Tumor growth inhibition of quizartinib as a single agent was 17.8% and 53.3% in the 0.5 mg/kg/dose and 1 mg/kg/dose groups, respectively. Tumor growth inhibition of DS-3032b in combination with quizartinib was 61.7% in the 25 mg/kg/dose + 0.5 mg/kg/dose group, 91.2% in the 50 mg/kg/dose + 0.5 mg/kg/dose group, 85.6% in the 25 mg/kg/dose + 1 mg/kg/dose group, and 97.5% in the 50 mg/kg/dose + 1 mg/kg/dose group. Estimated tumor volume was significantly lower in individual DS-3032b and quizartinib combination groups than in individual single gent groups of DS-3032b and quizartinib.

In the assessment of the combination of DS-3032b (orally given once daily for 11 days) and 5-azacytidine (intravenously given once daily for 5 days), tumor growth inhibition of DS-3032b as a single agent was 46.4% and 80.3% in the 25 mg/kg/dose and 50 mg/kg/dose groups, respectively, and tumor growth inhibition of 5-azacytidine as a single agent (4 mg/kg/dose) was 49.9%. Tumor growth inhibition of DS-3032b in combination with 5-azacytidine was 75.4% in the 25 mg/kg/dose + 4 mg/kg/dose group and 94.8% in the 50 mg/kg/dose + 4 mg/kg/dose group. Estimated tumor volume was significantly lower in individual DS-3032b and 5-azacytidine combination groups than in individual single agent groups of DS-3032b and 5-azacytidine.

1.2.2. Safety Pharmacology

DS-3032b was assessed for potential effects on the cardiovascular, respiratory, and central nervous systems.

In the study that assessed the potential effects of DS-3032b on the cardiovascular system, DS-3032b inhibited the human ether-a-go-go related gene (hERG) current at a concentration of 2.6 μM, inferring that the concentration causing 50% inhibition (IC_{50}) of DS-3032b against hERG current is greater than 2.6 μM. The statistically significant hERG current inhibitory concentration (2.6 μM) was approximately 200 times the maximum plasma concentration (Cmax; 0.013 μM) at the lethal dose of DS-3032a (free form), 460 times the IC_{50} value of DS-3032b for the MDM2-p53 interaction in vitro (0.00557 μM), and 9 to 60 times the concentration causing 50% growth inhibition (GI_{50}) values in in vitro pharmacology studies (0.043 μM to 0.276 μM). Moreover, the hERG channel was not significantly inhibited at 0.8 μM (approximately 60 times the free form Cmax at the lethal dose). In telemeterized male beagle dogs, no effects on clinical signs, or hemodynamic and electrocardiogram (ECG) parameters through 25 hours post-dose were observed at doses up to 10 mg/kg (lethal dose in a 4-week repeated-dose toxicity study). In addition, no effects on ECG parameters, heart rate, or waveform morphology (including corrected QT interval), as determined by surface leads, were seen in male or female dogs given repeated oral doses of 3 mg/kg/day for 3 months. These in vitro and in vivo data suggest a low potential risk on cardiovascular function in humans at DS-3032a exposures expected to be associated with clinical efficacy.

Effects of DS-3032b on the central nervous system (CNS) were assessed on Day 3 in male Sprague Dawley rats given up to 1000 mg/kg/day. Transient and reversible DS-3032b-related effects on motor activity were observed in male rats given 1000 mg/kg/day. However, the changes were relatively mild and were therefore assessed to be toxicologically insignificant.

Effects of DS-3032b on the pulmonary system were assessed on Day 1 in male Sprague Dawley rats given up to 1000 mg/kg/day. Transient and reversible increases in respiratory rate were observed in male rats given 1000 mg/kg/day. However, this effect was considered incidental because it was mild in severity and no statistically significant DS-3032b-related effects on minute volume were noted.

1.2.3. Pharmacokinetics and Drug Metabolism

In pharmacokinetic studies, plasma DS-3032a concentrations were assessed in male and female Sprague Dawley rats and beagle dogs orally given DS-3032a or DS-3032b. Exposures increased dose-dependently, and no accumulation of DS-3032a was noted after multiple dosing in either species, or rather, a decrease in exposures was found over time.

Pharmacokinetic exposures of DS-3032b in combination with anticancer drugs (quizartinib or 5-azacytidine) were assessed in in vivo pharmacology studies. Following administration of DS-3032b in combination with quizartinib in tumor-bearing mice, exposures increased with increasing dose of both DS-3032a and quizartinib. No apparent effect of drug-drug interactions between DS-3032a and quizartinib on exposures was observed. Exposures to each of DS-3032a and quizartinib tended to decrease after multiple doses. Following administration of DS-3032b in combination with 5-azacytidine in tumor-bearing mice, exposures to DS-3032a increased with increasing dose. No apparent effect of DS-3032b administration on 5-azacytidine exposure was observed. DS-3032a exposures tended to decrease by 5-azacytidine administration.

DS-3032a highly binds to proteins in mouse, rat, dog, and human plasma. Plasma protein binding was lowest in human plasma and was not concentration-dependent in all tested species.

DS-3032b was assessed for inhibition potential of human cytochrome P450 (CYP) isoforms by measuring metabolic activity of isoform-specific substrates using pooled human liver microsomes. DS-3032b showed direct inhibitory effects on CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5, but not on CYP1A2 or CYP2E1. DS-3032b also showed mild-to-moderate, metabolism-dependent inhibitory effects on CYP3A4/5 but not on the other CYP isoforms tested in this study. Meanwhile, DS-3032b was assessed for induction potential of CYP3A4, CYP1A2, and CYP2B6 using freshly isolated human hepatocytes from 3 individual donors. DS-3032b did not markedly change the messenger ribonucleic acid (mRNA) levels or enzyme activity of CYP1A2. DS-3032b weakly induced CYP3A4 as measured by mRNA levels and enzyme activity in 1 of 3 donors. As for CYP2B6, treatment with DS-3032b did not increase the mRNA levels or the enzyme activity, but rather decreased both levels. These data suggest that coadministered of DS-3032b with strong CYP3A4/5 inducers or inhibitors should be avoided in this Phase 1 study.

1.2.4. Toxicology

No serious toxicological changes were observed in rats given once-daily repeated oral doses up to 1000 mg/kg for 4 weeks. All changes in blood chemistry tests and organ weight measurement were fairly mild, with no histopathological findings. Therefore, these changes were considered to be toxicologically insignificant and were reversible during the recovery period. In rats given repeated oral doses for 4 weeks, the no observed adverse effect level (NOAEL) of DS-3032b was 1000 mg/kg/day. At this dose, Cmax of DS-3032b on Day 28 of the dosing period was 4820 ng/mL in males and 6627 ng/mL in females, and AUC24h was 57,719 ng·h/mL in males and 73,440 ng·h/mL in females. The severely toxic dose in 10% of the animals (STD_{10}) of DS-3032b was considered to be greater than 1000 mg/kg/day in rats.

In a 3-month repeated-dose toxicity study in rats, weight loss and decreased food consumption were observed in males given 1000 mg/kg. No treatment-related adverse changes were observed in any of the other examinations or in females. The NOAEL was 300 mg/kg/day for males and 1000 mg/kg/day for females. At the NOAEL, the mean Cmax and AUC24h values of DS-3032a on Day 91 of the dosing period were 2700 ng/mL and 24,800 ng·h/mL, respectively, in males, and 5050 ng/mL and 66,400 ng·h/mL, respectively, in females.

No serious toxicological changes were observed in dogs given once-daily, repeated oral doses up to 3 mg/kg for 4 weeks. In dogs given 10 mg/kg, weight loss was observed during the first week of the dosing period and clinical signs of toxicity (eg, emaciation, dehydration, hypoactivity, hunched position, decreased/no food consumption, liquid/unformed feces, and pyrexia) were also noted, and they were moribund and sacrificed on Day 11 or Day 12 of the dosing period, or on Day 4 of the recovery period. In dogs sacrificed on Day 11 or Day 12, neutropenia was observed, and clinical pathology findings included pancytopenia with bone marrow suppression, hemorrhage in multiple organs, and lymphocyte depletion in lymphoid organs. At lower doses (≤ 3 mg/kg), minimally to mildly decreased reticulocyte and platelet counts in males and females and transient decreases in white blood cell, neutrophil, and monocyte counts in males were observed on Day 12. These changes were not observed on Day 19 or Day 26 of the dosing period or during the recovery period. These slight and transient changes were therefore considered to be toxicologically insignificant. In dogs given repeated oral doses for 4 weeks, the NOAEL and the highest nonseverely toxic dose (HNSTD) of DS-3032b were 3 mg/kg/day. At this dose, Cmax of DS-3032b at Week 4 of the dosing period was 99.3 ng/mL in males and 84.9 ng/mL in females, and AUC24h was 973 ng·h/mL in males and 880 ng·h/mL in females.

In a 3-month repeated-dose toxicity study in dogs, one male in the 3 mg/kg group was found to have deteriorating conditions from Day 24 and was sacrificed on Day 27 of the dosing period. Suppression of the bone marrow and immune system was detected as test article-related histopathological changes, and this was considered to have caused hematological changes including decreases in leukocyte parameters and platelet count, and pathological changes including hemorrhage in several organs. In surviving male and female animals, a decrease in platelet count was noted in the 3 mg/kg group. In dogs given once-daily, repeated oral doses for 3 months, the NOAEL of DS-3032b was

determined to be 1 mg/kg/day in both males and females. The HNSTD of DS-3032b was considered to be 1 mg/kg/day for males and 3 mg/kg/day for females. At the NOAEL, the mean Cmax and AUC24h values of DS-3032a on Day 91 of the dosing period were 92.4 ng/mL and 1360 ng·h/mL, respectively, in males, and 94.7 ng/mL and 1170 ng·h/mL, respectively, in females.

DS-3032b showed negative results in all genotoxicity studies, including the bacterial reverse mutation study, in vitro micronucleus study in Chinese hamster lung (CHL) cells, and in vivo rat bone marrow micronucleus study. Accordingly, DS-3032b was concluded to have no genotoxic potential.

DS-3032b was found to be non-phototoxic in mouse (BALB/c 3T3 clone A31) fibroblasts using the neutral red uptake (NRU) assay, with a photo irritation factor (PIF) value of 1.396.

DS-3032b was assessed for myelotoxic potential in an in vitro progenitor cell (colony forming unit-granulocyte/macrophage [CFU-GM]) toxicity study in canine and human bone marrow specimens. DS-3032b inhibited CFU-GM with an IC_{50} of 32.2 nM, IC_{75} of 58.1 nM, and IC_{90} of 103.1 nM in canine bone marrow cultures, and with an IC_{50} of 220.2 nM, IC_{75} of 392.1 nM, and IC_{90} of 617.3 nM in human bone marrow cultures. Canine bone marrow was approximately 6- to 7-fold more sensitive to DS-3032b than human bone marrow.

1.3. Summary of Significant Findings Obtained from Previous Clinical Studies

1.3.1. Overseas Phase 1 Studies (Study DS3032-A-U101 and Study DS3032-A-U102)

DS3032-A-U101 is a Phase 1, multicenter, open-label study of DS-3032b in subjects with solid tumors or lymphomas, which are refractory to standard therapies or for which no standard treatment is available. This study consists of Part 1 (dose escalation) and Part 2 (dose expansion). The objectives of Part 1 were to evaluate the safety and tolerability of DS-3032b and assess the maximum tolerated dose (MTD) or the recommended phase 2 dose (RP2D) of DS-3032b. The objectives of Part 2 were to evaluate preliminary tumor response in subjects with advanced melanoma and subjects with diffuse large B-cell lymphoma (DLBCL). As of 31 Oct 2016, 69 subjects have been treated with DS-3032b in this study (49 subjects in the dose escalation part [Part 1] and 20 subjects in the dose expansion part [Part 2]), and 9 subjects are ongoing in the study. In Part 1, DS-3032b was administered once daily on Days 1 to 21, followed by a 7-day rest, in a 28-day cycle (qd 21/28 day schedule), starting from 15 mg and escalating through 30, 60, 120, 160 and 240 mg, guided by a modified continual reassessment method (mCRM) incorporating the escalation with overdose control (EWOC) principle. Dose-limiting toxicities (DLTs) were reported as Grade 4 thrombocytopenia and Grade 4 febrile neutropenia in 1 subject treated at 240 mg, and the study was continued at a reduced dose of 160 mg. At 160 mg, DLTs were reported as Grade 3 anorexia, nausea, and vomiting in 1 subject and Grade 4 neutropenia and Grade 2 thrombocytopenia in 1 subject. As a result, the study was continued at a further reduced dose of 120 mg. At

120 mg, DLTs were reported as Grade 4 thrombocytopenia in 1 subject and Grade 2 thrombocytopenia requiring dose interruption for more than 7 days in 1 subject.[12] Based on these results, the MTD for the qd 21/28 day schedule was determined to be 120 mg. Another dosing schedule was also evaluated in parallel where DS-3032b was administered in a 90 mg qd 28/28 day schedule. Grade 3 thrombocytopenia was reported as DLT in 1 subject treated on this dosing schedule.[12] The MTD for the qd 28/28 day schedule was therefore determined to be 90 mg. In the efficacy assessment, the best tumor response was stable disease (SD) in 27 of 35 subjects in Part 1 who had at least one post-dose tumor assessment. However, none of the subjects in this study have achieved an objective response (CR or partial remission [PR]) to date.

DS3032-A-U102 was a Phase 1, multicenter, open-label study of DS-3032b. This study, consisting of Part 1 (dose escalation) and Part 2 (dose expansion), was conducted in subjects with advanced hematological malignant tumors (AML, acute lymphocytic leukemia [ALL], chronic myelogenous leukemia [CML], and high-risk myelodysplastic syndrome [MDS]) to evaluate the safety and tolerability of DS-3032b, to assess the MTD or RP2D of DS-3032b, and to evaluate the pharmacokinetics/pharmacodynamics of DS-3032b. As of 17 Oct 2016, 37 subjects with AML or high-risk MDS have been enrolled and treated with DS-3032b in the dose escalation part (Part 1), and the study is currently underway. In Part 1, DS-3032b was administered once daily on Days 1 to 21, followed by a 7-day rest, in a 28-day cycle (qd 21/28 day schedule), starting from 60 mg and escalating through 90, 120, 160 and 210 mg, guided by mCRM with EWOC. DLTs were reported as Grade 3 hypokalemia in 1 subject and Grade 3 diarrhea in 1 subject at 160 mg. At 210 mg, DLTs were reported as Grade 2 acute renal failure (less than 75% of the specified number of dosing days in Cycle 1), Grade 3 nausea and vomiting, and Grade 3 fatigue and anorexia in 1 subject each.[13] Based on these results, MTD for the qd 21/28 day schedule was determined to be 160 mg. In the efficacy assessment, a decrease in bone marrow blasts (≥50% decrease from baseline in 10 of 15 subjects) was observed in 15 of 26 subjects who underwent bone marrow assessment 28 days after the first dose of DS-3032b (after the end of the first cycle). CR was achieved in 2 subjects with relapsed or refractory AML who were treated with DS-3032b at 120 mg qd for 4 months or 160 mg qd for 13 months, and CR as determined by bone marrow assessment was achieved in 1 subject with high-risk MDS who was treated with DS-3032b at 120 mg qd for 4 months.[13]

1.3.2. Japanese Phase 1 Study (Study DS3032-A-J103)

DS3032-A-J103 is a Phase 1 dose-ascending study of DS-3032b in Japanese subjects with advanced solid tumors or lymphomas. The objectives of the study were to evaluate the safety and tolerability of DS-3032b, assess the MTD or RP2D of DS-3032b, and evaluate the pharmacokinetics and pharmacodynamics of DS-3032b.

In this study, DS-3032b was administered once daily on Days 1 to 21, followed by a 7-day rest, in a 28-day cycle (qd 21/28 day schedule), starting from 60 mg and escalating through 90 mg and 120 mg, guided by mCRM with EWOC. As of 31 Oct 2016, a total of 18 subjects have been enrolled and treated in the study, and the study is currently underway. DLTs were reported in subjects treated at 120 mg, and the MTD for the qd 21/28 day schedule was determined to be 90 mg.

1.4. Known and Foreseeable Risks

DS-3032b was studied for potential toxicity in rats and dogs. In the 4-week repeated-dose toxicity study in rats, DS-3032b was well tolerated up to 1000 mg/kg (the highest dose tested). In the 3-month oral dose study, DS-3032b was well tolerated up to 300 mg/kg in males and 1000 mg/kg (the highest dose tested) in females. Weight loss and decreased food consumption were observed in males at 1000 mg/kg. In the 4-week repeated-dose toxicity study in dogs, DS-3032b was well tolerated at 3 mg/kg given as repeated oral doses. DS-3032b given as repeated oral doses of 10 mg/kg/day (the highest dose tested) was associated with moribund condition in the observation of clinical signs, with neutropenia, moderate to severe pancytopenia with bone marrow suppression, hemorrhage in multiple organs, and lymphocyte depletion in lymphoid organs. Effects on bone marrow and lymphoid tissues were predictable from pharmacology studies of DS-3032b. These results showed the primary target effects of DS-3032b on the hematopoietic/lymphoid system in dogs. In the 3-month repeated-dose toxicity study in dogs, DS-3032b was given as repeated oral doses of 3 mg/kg (the highest dose tested), and pancytopenia, suppression of the bone marrow and immune system, and hemorrhages in several organs were observed in 1 sacrificed male. In the surviving animals, a decrease in platelet counts was noted in males and females in the 3 mg/kg group.

Several reports are available for clinical studies using drugs that inhibit the MDM2-p53 interaction. According to published clinical data of MDM2 antagonists such as RG7112,[14] RG7388,[15] and SAR405838,[16] adverse events (AE) of blood and lymphatic system disorders and gastrointestinal disorders have been reported.

In DS3032-A-U101, an overseas study in subjects with advanced solid tumors or lymphomas, treatment emergent adverse events (TEAEs) reported in more than 10% of a total of 69 subjects who have been treated as of 31 Oct 2016 were nausea in 47 subjects (68.1%), thrombocytopenia in 22 subjects (31.98%), platelet count decreased in 22 subjects (31.9%), fatigue in 35 subjects (50.7%), anaemia in 30 subjects (43.5%), diarrhoea in 27 subjects (39.1%), decreased appetite in 26 subjects (37.7%), white cell count decreased in 19 subjects (27.5%), leukopenia in 5 subjects (7.2%), neutropenia in 9 subjects (13.0%), neutrophil count decreased in 11 subjects (15.9%), vomiting in 20 subjects (29%), constipation in 16 subjects (23.2%), dysgeusia in 14 subjects (20.3%), cough in 14 subjects (20.3%), dyspnoea in 12 subjects (17.4%), headache in 11 subjects (15.9%), abdominal pain in 10 subjects (14.5%), dizziness and alopecia in 7 subjects (10.1%) each, and dry mouth and peripheral oedema in 9 subjects (13.0%) each. Reported DLTs were Grade 4 thrombocytopenia and Grade 4 febrile neutropenia in 1 subject in the 240 mg qd group (21/28 day schedule), and Grade 3 anorexia, nausea, and vomiting in 1 subject and Grade 4 neutropenia and Grade 2 thrombocytopenia in 1 subject in the 160 mg qd group (21/28 day schedule). DLTs reported in the 120 mg qd group (21/28 day schedule) were Grade 4 thrombocytopenia in 1 subject and Grade 2 thrombocytopenia requiring dose interruption for more than 7 days in 1 subject. Grade 3 thrombocytopenia was also reported in 1 subject in the 90 mg qd 28/28 day schedule.[12]
In DS3032-A-U102, an overseas study in subjects with advanced hematological malignant tumors, TEAEs reported in more than 10% of a total of 37 subjects who have been treated as of 17 Oct 2016 were nausea in 28 subjects (75.7%), diarrhoea in 21

subjects (56.8%), fatigue in 16 subjects (43.2%), vomiting in 13 subjects (35.1%), thrombocytopenia in 13 subjects (35.1%), anaemia in 12 subjects (32.4%), decreased appetite in 10 subjects (27%), hypotension in 10 subjects (27%), hypokalaemia in 9 subjects (24.3%), neutropenia in 9 subjects (24.3%), febrile neutropenia, pneumonia, hypomagnesaemia, and peripheral oedema in 6 subjects (16.2%) each, asthenia, dizziness, and dyspnoea in 5 subjects (13.5%) each, and pyrexia, dehydration, and hyperuricemia in 4 subjects (10.8%) each. DLTs reported in the 160 mg qd group (21/28 day schedule) were Grade 3 hypokalemia in 1 subject and Grade 3 diarrhea in 1 subject. DLTs reported in the 210 mg group (21/28 day schedule) were Grade 2 acute renal failure (less than 75% of the specified number of dosing days in Cycle 1), Grade 3 nausea and vomiting, and Grade 3 fatigue and anorexia in 1 subject each.[13] In DS3032-A-J103, a Japanese study in subjects with advanced solid tumors or lymphomas, TEAEs reported in more than 10% of a total of 18 subjects who have been treated as of 31 Oct 2016 were nausea in 13 subjects (72.2%), decreased appetite in 11 subjects (61.1%), fatigue in 9 subjects (50%), white blood cell count decreased in 9 subjects (50%), hypoalbuminaemia in 7 subjects (38.9%), anaemia in 6 subjects (33.3%), platelet count decreased in 6 subjects (33.3%), constipation, diarrhoea, and vomiting in 5 subjects (27.8%) each, hyponatremia, ALT increased, and AST increased in 4 subjects (22.2%) each, thrombocytopenia, pyrexia, lymphocyte count decreased, neutrophil count decreased, and hypophosphatemia in 3 subjects (16.7%) each, and insomnia, cough, dry skin, proteinuria, and weight decreased in 2 subjects (11.1%) each. It is predicted from these results that DS-3032b may cause AEs of gastrointestinal disorders and blood and lymphatic system disorders. Patients treated with DS-3032b should therefore be closely monitored throughout the study period, and if any of these AEs occur, measures should be taken immediately.

Nonclinical data also suggest that coadministration of DS-3032b with CYP3A4/5 inhibitors or inducers may confound the metabolism of DS-3032b. Concomitant use of CYP3A4/5 inhibitors and inducers is therefore prohibited in this study.

2. STUDY OBJECTIVES

Primary Objective:

To evaluate the safety and tolerability of DS-3032b monotherapy administered as multiple doses and assess the MTD in Japanese subjects with relapsed or refractory AML.

Secondary Objectives:

- To evaluate the pharmacokinetics of DS-3032a
- To exploratively evaluate the antitumor effect of DS-3032b

Exploratory Objectives:

- To evaluate the pharmacodynamic effect of DS-3032b on macrophage inhibitory cytokine-1 (MIC-1) levels in serum
- To confirm if a *TP53* mutation is present or not using bone marrow and blood specimens
- To evaluate biomarker candidates related to the action mechanism of DS-3032b using bone marrow and blood specimens
- To assess the recommended dose in subsequent phases of development

3. STUDY DESIGN

This is a Phase 1, multicenter, open-label uncontrolled study. Combinations of doses and dosing schedules are shown in "Figure 3.1 Combinations of Doses and Dosing Schedules." Four dose-finding Subtrials (Subtrials A, B, C, and D) of DS-3032b will be conducted by fixing the dosing schedule. The study will be started from Subtrial A, and other subtrials will be conducted as necessary.

In Subtrials A, B, and D, the study drug will be administered once daily (qd) on Days 1 to 14, Days 1 to 7, and Days 1 to 21, followed by a 14-day, 21-day, and 7-day rest, respectively, in a 28-day cycle. In Subtrial C, the study drug will be administered once daily (qd) on Days 1 to 3, followed by a 11-day rest, in a 14-day subcycle, which will be repeated twice in a 28-day cycle.

Subjects must be hospitalized in Cycle 1, which is the DLT evaluation period. The number of treatment cycles will not be specified, and the study treatment for each subject will be continued unless the criteria provided in "Section 5.6 Withdrawal Criteria " are met.

The MTD will be determined for each subtrial (see "Section 5.3.2 Definition of Maximum Tolerated Dose").

Figure 3.1: Combinations of Doses and Dosing Schedules

Dose (mg)	Subtrial C	Subtrial B	Subtrial A	Subtrial D
160	C-3	B-3	A-3	D-3
120	C-2	B-2	A-2	D-2
90	C-1	B-1	A-1	D-1
	3/14 × 2	7/28	14/28	21/28
	Dosing schedule (day/day)			

3.1. Starting Dose in Each Subtrial

The dose of DS-3032b for Cohort 1 in Subtrial A will be 90 mg (see "Section 5.2.3 Rationale for the Dose and Regimen").

The starting dose in the subtrial that has a smaller number of dosing days than the subtrial in which the MTD has been determined will be equal to or lower than the MTD in the subtrial in which the MTD has been determined. For instance, when the MTD in Subtrial A is determined to be 120 mg, the starting dose in Subtrial B will be 120 mg or 90 mg.

The starting dose in the subtrial that has a greater number of dosing days than the subtrial in which the MTD has been determined will be lower than the MTD in the subtrial in which the MTD has been determined. For instance, when the MTD in Subtrial A is determined to be 160 mg, the starting dose in Subtrial D will be 120 mg or 90 mg. When the MTD has not been reached in Subtrial A, the starting dose in Subtrial D will be equal to or lower than the maximum dose used in Subtrial A.

3.2. Explorative Dose Finding in Each Subtrial

After confirming the DLT rate in Cycle 1 in each cohort in accordance with "Section 5.3.1 Definition of Dose-limiting Toxicities," the dose for the next and subsequent cohorts will be determined, in consideration of the following i) and ii). As a rule, each cohort consists of 3 to 6 subjects, and if "Section 5.4 Enrollment of Additional Subjects " is applicable, enrollment of additional subjects will be considered.

i) Recommended dose, guided by mCRM using a Bayesian logistic regression model (BLRM) incorporating the EWOC principle

ii) Clinical evaluation of the toxicological profile and information on pharmacokinetics/pharmacodynamics (PK/PDy)

Rationale:

The study design was selected in reference to the "Guidelines for Clinical Evaluation of Anticancer Drugs.[17]" The Bayesian statistical analysis methods are specified in "Section 11.7 Details of Modified Continual Reassessment Method."

4. STUDY POPULATION

4.1. Selection of Subjects

Subjects who satisfy all of the following inclusion criteria and do not meet any of the exclusion criteria are eligible for this study.

4.1.1. Inclusion Criteria

1. Provision of written informed consent for participation in this study.
2. Age ≥20 years old upon enrollment in this study.
3. Having AML (including those with a history of MDS) satisfying either of the following:
   i) Have failed to achieve remission with at least 1 cycle of prior induction therapy
   ii) Have relapsed after achieving remission with prior therapy
4. Those who appear unable to achieve persistent remission with standard treatment, who failed to complete potentially curative treatment, or who have no treatment options with expected therapeutic efficacy.
5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2 (refer to "Appendix 2").
6. Having laboratory data satisfying all of the following criteria in the measurement within 14 days before enrollment in this study.

Laboratory Parameter	Requirement
AST	≤2.5 × the upper limit of normal of the center (ULN)
ALT	≤2.5 × ULN
Total bilirubin	≤1.5 × ULN
Serum creatinine	Creatinine clearance ≥60 mL/min, as calculated using the modified Cockcroft Gault equation* In case of creatinine clearance ≥50 mL/min and <60 mL/min, as calculated using the above equation, the subject may be enrolled if the serum creatinine level is ≤1.5 × ULN.
Prothrombin time-international normalized ratio (PT-INR)	≤1.5 × ULN
Activated partial thromboplastin time (aPTT)	≤1.5 × ULN

*: ([140 − age (year)] × [actual weight (kg)]) / [72 × serum creatinine (mg/dL)] (× 0.85 [if female])

7. Able to take the following interval during the period from the last dose or last procedure of prior therapy to the start day of treatment with the study drug (study treatment) in this study.
   i) Cytotoxic drugs: 2 weeks (48 hours for hydroxycarbamide used for the purpose of controlling the increase in white blood cells)
   ii) Non-cytotoxic drugs: At least 5 times the half-life of the drug
8. Women of childbearing potential must have a negative pregnancy test at screening and must be willing to use highly effective birth control (eg, barrier contraceptives with spermicides, intrauterine device) during the following period: Upon enrollment, during the treatment period, and for at least 95 days after the last dose of DS-3032b. Women of childbearing potential are those in the period from first menstruation to menopause (no menstrual period for a minimum of 12 months). This, however, shall exclude permanently (surgically) sterile women.
9. Males must be surgically sterile or willing to use highly effective birth control upon enrollment, during the treatment period, and for at least 95 days after the last dose of DS-3032b. Male subjects may not donate their sperm during the study period and for at least 95 days after the last dose of DS-3032b.
10. Able to be hospitalized during the DLT evaluation period.

Rationale:

1. To ensure the eligibility of study subjects, and in consideration of ethics.
2. The lower limit of age is 20 years at which each subject can provide informed consent appropriately based on his/her own judgment.

3, 5, 10. To appropriately evaluate the safety of DS-3032b.

4. As recommended in the Guidelines for the Clinical Evaluation of Anticancer Drugs.[17]
6. To confirm that the subjects have adequate organ functions for appropriate evaluation of the subject's safety, as recommended in the Guidelines for the Clinical Evaluation of Anticancer Drugs.[17]
7. To confirm that the subjects are in a stable physiological condition at registration, as recommended in the Guidelines for the Clinical Evaluation of Anticancer Drugs.[17]

8, 9. Since an effect of DS-3032b on fetuses or infants cannot be ruled out. Breastfeeding women are not allowed to participate in this study independent of whether or not they temporarily discontinue breastfeeding.

4.1.2. Exclusion Criteria

1. Diagnosis of acute promyelocytic leukemia.

2. Chronic myeloid leukemia in blast crisis (positive for a breakpoint cluster region-c-Abelson [BCR-ABL] fusion gene).
3. History of or concurrent central nervous system leukemia.
4. History of hematopoietic stem cell transplant (HSCT) and meeting any of the following:
   i) Transplantation within 60 days before the start of study treatment
   ii) Persistent graft-versus-host disease (GVHD) that is clinically significant, requires the start of treatment, or requires intensification of treatment within 21 days before informed consent
   iii) Persistent Grade ≥2 clinically significant or irreversible non-hematological toxicity related to transplantation
5. Uncontrolled infection requiring intravenous antibiotics, antifungals, or antivirals.
6. A positive test result for hepatitis C virus (HCV) antibody or human immunodeficiency virus (HIV) antibody within 90 days before enrollment.
7. A positive test result for hepatitis B surface (HBs) antigen within 90 days before enrollment.
8. A positive test result for hepatitis B core (HBc) antibody or HBs antibody with hepatitis B virus (HBV)-DNA levels ≥2.1 log copies/mL, despite a negative test result for HBs antigen, within 90 days before enrollment.
9. Receiving strong CYP3A inhibitors within 7 days before the start of study treatment.
10. Receiving strong CYP3A inducers within 14 days before the start of study treatment.
11. History of or current cardiovascular disease as specified below:
    i) QT corrected for heart rate using Fridericia's method (QTcF) interval >450 ms, determined as the average of triplicate ECG measurements taken within 14 days before enrollment in this study
    ii) Class III or more severe congestive heart failure according to "Appendix 3 New York Heart Association (NYHA) Functional Classification" within 6 months before enrollment in this study
    iii) History of myocardial infarction within 6 months before enrollment in this study
    iv) History of angina pectoris attack within 6 months before enrollment in this study
    v) History of arrhythmia requiring treatment within 6 months before enrollment in this study
    vi) Need for a pacemaker or implantable cardioverter defibrillator
    vii) Diagnosed or suspected congenital long QT syndrome

viii) History of life-threatening ventricular arrhythmia (ventricular tachycardia, ventricular fibrillation, or torsades de pointes)

ix) History of bradyarrhythmia (eg, atrioventricular block)

x) Clinically significant electrolyte abnormalities that can induce secondary long QT syndrome

xi) Uncontrolled hypertension despite pharmacotherapy etc.

12. Adverse drug reactions (excluding alopecia) to previous therapy (treatment for AML and/or anticancer therapy), which have not resolved or returned to Grade 1 or baseline. Patients with chronic Grade 2 adverse drug reactions (eg, chemotherapy-induced neuropathy) may be eligible when the investigator or subinvestigator decides that there are no clinical safety concerns from the standpoint of the patient's safety.

    * The grade will be assessed according to the "Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0."

13. History of another malignant tumor requiring treatment within 2 years before enrollment in this study.

    However, patients whose disease is considered to have been cured by local treatment (eg, non-melanoma skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast) may be eligible for participation in the study.

14. Predisposition to serious infection (eg, cystic fibrosis, congenital or acquired immunologic disease, hemorrhagic disease, or cytopenia unrelated to AML).
15. Disseminated intravascular coagulation or other clinically significant coagulation abnormalities.
16. Extensive surgery within 28 days before the start of study treatment.
17. Radiation therapy within 28 days before the start of study treatment.
18. Any factor that could preclude adequate absorption of DS-3032b (eg, refractory nausea and vomiting, malabsorption, biliary shunt, significant bowel resection, and/or GVHD affecting the gut).
19. Pregnant or breastfeeding women.
20. Patients who are otherwise considered ineligible for the study in the opinion of the investigator or subinvestigator.

Rationale:

1 to 18. To appropriately evaluate the safety of DS-3032b.

19. Since an effect of DS-3032b on fetuses or infants cannot be ruled out. Breastfeeding women are not allowed to participate in this study independent of whether or not they temporarily discontinue breastfeeding.

20. To allow the investigator or subinvestigator to determine the subject's eligibility for participation in the study from a comprehensive standpoint, including careful consideration of the subject's safety.

4.1.3. Registration of Subjects

Subjects will be registered in the study according to the procedure described below.

4.1.3.1. Flow of Subject Registration

After obtaining written informed consent from subjects, the investigator or subinvestigator will assign a subject identification code to each of the subjects. The investigator or subinvestigator will fill out the Subject Registration Form for subjects who are assessed to be eligible for the study among the above subjects and send it by fax to the sponsor.

The sponsor will confirm the eligibility of the concerned subjects against the inclusion and exclusion criteria for this study based on the information in the received Subject Registration Form. If there are any questions about the information in the Subject Registration Form, the sponsor will immediately contact the investigator or subinvestigator for confirmation. Subjects who are assessed to be eligible for the study by the sponsor will be registered in this study and assigned a subject number.

The sponsor will immediately fax the registration confirmation form with the result of eligibility assessment to the investigator; the confirmation form should include the date of registration, subject number, and dose of the study drug for subjects assessed to be eligible, and the fact that the subject is not eligible and the reason for subjects assessed to be ineligible. The investigator or subinvestigator will explain the reason for ineligibility to subjects who are assessed to be ineligible for the study by the sponsor.

Address for sending the Subject Registration Form
(the sponsor's address)
Working hours: Monday to Friday, 9:00 to 17:30
(closed on Saturdays, Sundays, and public holidays)
FAX: PPD
TEL: PPD

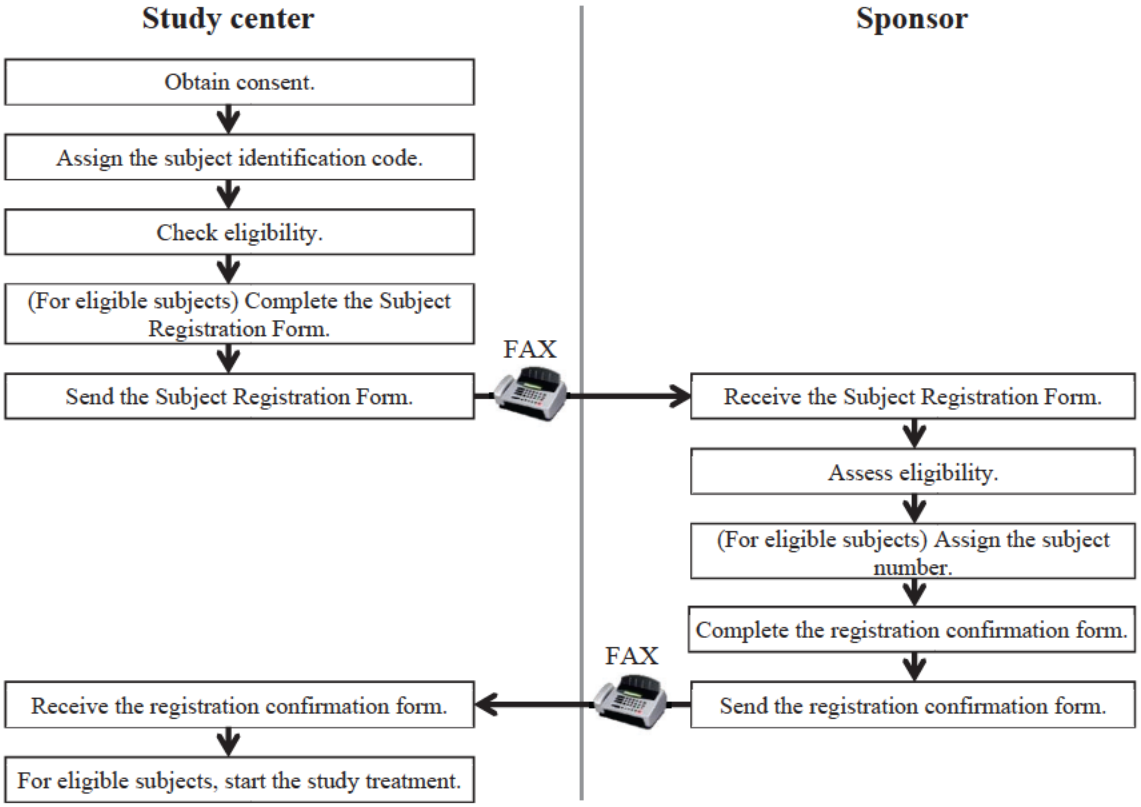
The investigator or subinvestigator must not prescribe the study drug before registration of subjects.

If there is any subject who has provided informed consent, but is not registered in the study, the investigator or subinvestigator will record the reason why the concerned subject has not been registered in the medical record. Such a subject will not be included in the number of subjects enrolled in this study.

If a subject who has provided informed consent, but is assessed to be ineligible for the study at the time of eligibility confirmation and for whom a Subject Registration Form has not been faxed to the sponsor, is confirmed to satisfy the eligibility criteria at a later date, the investigator or subinvestigator may fax the Subject Registration Form to the

sponsor after re-obtaining written informed consent to participate in this study from the concerned subject.

Figure 4.1-1: Subject Registration Procedure



4.1.3.2. Notifying Any Other Physicians Treating Subjects of Their Study Participation

The investigator or subinvestigator will ask subjects who have provided informed consent whether they are being treated by another physician (eg, a physician in another department of the study center or at another medical institution) or not. If the subject is receiving treatment by another physician, the investigator or subinvestigator will inform the physician of the subject's participation in the study with the subject's approval and record the information in the medical record.

4.2. Subject Withdrawal Criteria and Procedure at Withdrawal

If a subject meets "Section 5.6 Withdrawal Criteria" while participating in this study, the investigator or subinvestigator will discontinue the study treatment for the concerned subject, and perform the examinations and assessments in accordance with "Section 6.4 Procedures at Study Discontinuation." The investigator or subinvestigator will record the date of discontinuation, reason for discontinuation, examination and investigation results in the case report form.

5. METHODOLOGY

5.1. Study Drug

For the details of the study drug and its handling, see the "Investigator's Brochure" and "Procedure for Study Drug Management."

1. Investigational substance code: DS-3032b
2. Generic name: milademetan
3. Content and dosage form:

   White opaque capsules, each of which contains 30 mg of DS-3032b as the free form of its drug substance, or white opaque, red-lined capsules, each of which contains 100 mg of DS-3032b as the free form of its drug substance.
4. Lot number: Lot numbers are listed in the "Procedure for Study Drug Management."

5.1.1. Labeling and Packaging

Thirty five capsules of the study drug are packed with a desiccant agent in a plastic bottle. The information that should be included on the label is provided in Table 5.1.1 Descriptions on the Labeling of the Study Drug.

Table 5.1.1: Descriptions on the Labeling of the Study Drug

Labeled as "For Clinical Trial Use Only"
Study drug name
Protocol number
Study drug lot number
Storage conditions
Statement, "Do not discard but store unused study drug tablets; they will be collected later."
Name of the sponsor
Address of the sponsor

5.1.2. Storage of the Study Drug

After concluding the clinical study contract, the sponsor will distribute the study drug to the study center. The study drug manager will store and manage the study drugs, which are placed with a desiccant agent in plastic bottles, at up to 25°C (excursions permitted up to 30°C). The study drug will be managed and collected in accordance with the "Procedure for Study Drug Management."

5.2. Method of Study Treatment

5.2.1. Dose

The starting dose of DS-3032b in Subtrial A will be 90 mg. The subsequent doses will be determined, taking the following into consideration.

i) Recommended dose, guided by mCRM using a BLRM incorporating the EWOC principle

ii) Clinical evaluation of the toxicological profile and information on PK/PDy

Dose increments should be at least 1.3-fold in order to make a distinction among the dose cohorts, considering inter-subject variability in exposure. Even if the recommended dose for the next cohort calculated by the model is more than 2-fold, the dose should be no more than 2-fold.

5.2.2. Regimen

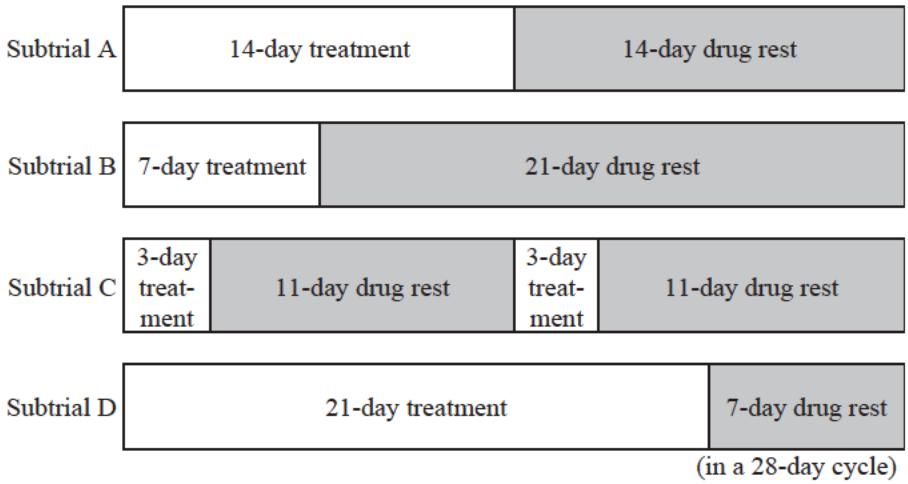
In Subtrial A, the study drug will be administered once daily on Days 1 to 14, followed by a 14-day rest, in a 28-day cycle (14/28 schedule). Each cycle is 28 days long. Capsules with two different strengths will be used as the study drug (30 mg and 100 mg). As a rule, subjects will orally take the study drug once daily every morning under fasting conditions. Meal consumption should be avoided from 2 hours before dosing to 1 hour after dosing.

The first dose of the study drug will be started within 7 days of the day of registration. If the study treatment is started on Day 8 or later from the day of registration, the first dose of the study drug should be started only after the subject's eligibility has been confirmed again before the start of the study treatment (see "Section 6.2 Study Procedures before Registration of Subjects"). Day 1 of Cycle 3 and subsequent cycles may be rescheduled within + 3 days of the originally scheduled date. If the schedule of Day 1 is changed, all subsequent scheduled dates will be changed accordingly.

If a subject vomits after taking the study drug, it is not allowed to take another dose of the study drug on the same day.

Other dosing schedules (Subtrials B, C, and D) will be assessed if it becomes necessary in order to evaluate the safety of DS-3032b. Dosing schedules in each subtrial are shown in "Figure 5.2-1 Dosing Schedules in Each Subtrial."

Figure 5.2-1: Dosing Schedules in Each Subtrial



5.2.3. Rationale for the Dose and Regimen

The dose and regimen of this study were established in reference to the results of the Phase 1 studies that are currently underway in the US and Japan. In DS3032-A-J103, a Japanese study of DS-3032b in subjects with solid tumors or lymphomas, the MTD was determined to be the 90 mg qd 21/28 day schedule. Based on this result, the starting dose for this study was determined to be 90 mg/day once daily. In DS3032-A-U102, an overseas study of DS-3032b in subjects with hematological malignant tumors, CR as determined by bone marrow assessment was achieved in 1 subject with high-risk MDS treated on the 160 mg qd 14/28 day schedule. The 14/28 day schedule is also adopted in another overseas clinical study that is currently underway. It was therefore considered appropriate to start the treatment on the 14/28 day schedule in this study. The study was designed to increase the dose based on the recommended dose guided by mCRM, with the planned maximum dose of 160 mg/day.

5.2.4. Randomization and Blinding

No randomization or blinding will be performed in this study.

5.3. Definition of Dose-limiting Toxicities and Maximum Tolerated Dose

5.3.1. Definition of Dose-limiting Toxicities

A DLT is defined as any Grade 3 or higher non-hematological AE unless related to the primary disease, course of the primary disease, complications, or concomitant medications, that occurs during the DLT evaluation period (28 days of Cycle 1), with the exceptions as defined below:

1. The following events will be assessed as DLTs:
    - Grade 4 aspartate aminotransferase (AST)/alanine aminotransferase (ALT)

- Grade 3 AST/ALT lasting ≥3 days, Grade 3 AST/ALT with Grade ≥2 total bilirubin
- Unable to complete at least 75% of the prescribed doses of DS-3032b in Cycle 1 (28 days) as a result of Grade ≥2 events

2. The following events will not be assessed as DLTs:

- Grade 3 fatigue lasting <3 days
- Grade 3 nausea or vomiting that has resolved to Grade ≤2 within 48 hours after antiemetic therapy
- Grade 3 diarrhea that has resolved to Grade ≤2 within 48 hours after antidiarrheal therapy
- Alopecia
- Febrile neutropenia
- Transient laboratory abnormalities that do not involve clinical symptoms and do not require continuous treatment (≥Grade 3 ALP, uric acid, amylase, and lipase, hyponatremia that has resolved within 72 hours after onset, etc.)

The following hematological toxicities will be assessed as DLTs.

- Failure to recover neutrophil count to ≥500 /mm^3 and platelet count to ≥20,000 /mm^3, leading to a delay in starting Cycle 2 for more than 2 weeks

5.3.2. Definition of Maximum Tolerated Dose

If any of the following completion criteria are met, the MTD will be determined based on comprehensive evaluation of the recommended dose guided by mCRM incorporating the EWOC principle, and safety and PK/PDy information of DS-3032b.

Completion criteria:

- DLT evaluation is completed in at least 15 subjects in the entire study and in at least 6 subjects in the cohort of the dose selected to be the dose for the next cohort by mCRM.
- DLT evaluation is completed in at least 6 subjects in the cohort of the dose selected to be the dose for the next cohort by mCRM, with at least 50% posterior probability for the DLT rate ranging between 16% and 33%.
- DLT evaluation is completed in at least 3 subjects in the cohort of each dose, with no DLTs reported.
- The posterior probability for the DLT rate of 33% or higher in the 90 mg cohort is at least 60%.

5.3.3. Study Treatment to Subjects in Each Cohort and Procedure for Proceeding to the Next Cohort

In the cohort of the first dose, study treatment for the second subject must be started after an at least 1-week interval from the first dose of treatment in the first subject. In the subsequent cohorts, study treatment for the next subject may be started on the following day of the start day of study treatment in the first subject.

If proceeding to the next cohort involves an increase in the dose, study treatment for the first subject in the new cohort will be started after the end of the DLT evaluation period in at least 3 subjects in the ongoing cohort. If a DLT occurs in 2 subjects before registration of the third subject, the dose for the third subject will be reviewed by using the mCRM incorporating the EWOC principle.

5.4. Enrollment of Additional Subjects

If there is a subject who cannot be evaluated for DLTs because of withdrawal from the study before the end of Cycle 1 for any reason during the study, additional subjects will be enrolled. In other cases where enrollment of additional subjects is considered necessary, whether or not to enroll additional subjects will be considered through discussion between the investigator and the sponsor. The medical expert may join the discussion as necessary.

5.5. Actions to be Taken for Adverse Events

If a toxicity that falls under the following definition occurs, dose interruption, postponement of the start of the next cycle (hereinafter, postponement), or dose reduction should be performed as shown below.

5.5.1. Occurrence of Dose-limiting Toxicities or Toxicities Equivalent to the Definition of Dose-limiting Toxicities after Cycle 1

If a DLT occurs or a treatment-related toxicity falling under the definition of DLTs occurs after Cycle 1, the investigator or subinvestigator should interrupt, postpone, or discontinue the study treatment. If the toxicity improves to Grade ≤1 or the subject recovers to the baseline condition, the investigator or subinvestigator will consider resuming the study treatment at a one-level reduced dose from the dose used in his/her participating cohort (in the case of the 90 mg cohort, resumption at a dose of 90 mg should be considered), only when it is considered beneficial to the subject. Once the dose is reduced, the dose should not be increased again.

The duration of dose interruption must not exceed 4 weeks. If the subject does not recover 4 weeks or more after the onset of the toxicity, the subject should be withdrawn from the study. In case a Grade ≥3 toxicity or a serious adverse event (SAE) that is apparently attributable to the primary disease occurs, the study treatment may be interrupted or postponed until the toxicity or the event improves to Grade ≤1 or until the subject recovers to the baseline condition.

5.5.2. Occurrence of the Following Toxicities Not Listed in Section 5.5.1

If any of the following toxicities, not listed in "Section 5.5.1 Occurrence of Dose-limiting Toxicities or Toxicities Equivalent to the Definition of Dose-limiting Toxicities after Cycle 1," occur, the investigator or subinvestigator will continue the study treatment if the toxicity can be controlled by appropriate intervention.

- Grade ≥2 non-hematological toxicity (excluding alopecia) unrelated to the primary disease, Grade ≥3 fatigue lasting >48 hours
- Grade ≥2 laboratory abnormalities not falling under the definition of DLTs
- Hypoplastic marrow (neutrophil count <500 /mm^3 and platelet count <20,000 /mm^3)

When it is considered necessary to interrupt or postpone the study treatment, interruption or postponement of the study treatment until the toxicity resolves to the following conditions will be considered. Resumption of the study treatment may be considered if the toxicity is confirmed to have improved or resolved within 4 weeks. When the study treatment is resumed, a reduction to the dose in the cohort that is one-level lower than the dose the pertinent subject was receiving before experiencing the toxicity will be considered.

- Neutrophil count ≥500 /mm^3
- Platelet count ≥20,000 /mm^3
- Grade ≥2 non-hematological toxicities (excluding alopecia) that have improved to Grade ≤1 or have resolved to baseline levels

5.6. Withdrawal Criteria

Subjects will be withdrawn from the study for the following reasons.

1. Apparent progression of the disease is found.
2. It becomes difficult to continue the study treatment due to AEs (refer to "Section 5.5 Actions to be Taken for Adverse Events").
3. A *TP53* mutation is detected after study treatment and it is decided inappropriate to continue the study for the subject.
4. The subject is found to be ineligible for the study after enrollment in the study.
5. The subject withdraws his/her consent to participation in the study.
6. The sponsor decides to prematurely terminate the study.
7. The subject has received the study drug on less than 75% of the specified number of dosing days in Cycle 1.
8. Other cases that the investigator or subinvestigator judges it inappropriate to continue the study for the subject.

If a subject is withdrawn from the study treatment, the investigator or subinvestigator will provide appropriate care to the subject, and record the date and reason of withdrawal in the case report form. The date of withdrawal from the study treatment will not be the date when the event leading to withdrawal occurs, but the date when the investigator or subinvestigator decides on withdrawal.

If a subject is withdrawn due to an AE, the investigator or subinvestigator will provide appropriate treatment to the subject and continue follow-up until resolution or relief of the AE as far as possible.

5.7. Prohibited Concomitant Drugs and Therapies, and Restricted Concomitant Drugs

5.7.1. Prohibited Concomitant Drugs and Therapies

- From informed consent to the day of the Follow-up:

  Anticancer treatment other than the study drug (excluding hydroxycarbamide), other investigational products, and investigational medical devices

- From 14 days before the start of study treatment to the day of the Follow-up:

  Strong CYP3A inducers and St. John's wort-containing foods and supplements

- From 7 days before the start of study treatment to the day of the Follow-up:

  Strong CYP3A inhibitors and grapefruit-containing foods and beverages

Rationale:

These specifications are provided with safety and ethical considerations for patients, and also to eliminate the effects of other drugs on this study as far as possible. Since nonclinical data indicate that DS-3032b is mainly metabolized by CYP3A, these specifications are necessary for the appropriate evaluation of the pharmacokinetics and safety of the study drug.

5.7.2. Restricted Concomitant Drugs

- Hydroxycarbamide should be used as per the following instructions.

  Use of hydroxycarbamide is prohibited during the period from 48 hours before treatment with DS-3032b to the start of treatment with DS-3032b. It is, however, allowed to concomitantly use hydroxycarbamide to control white blood cell counts at doses up to 5 g/day for a total of 8 days or less only during the period from after the start of treatment with DS-3032b to the end of the Follow-up.

- Prophylactic treatment for the following symptom is prohibited during the DLT evaluation period. However, treatment given as supportive care for the following symptom is allowed.

- Neutropenia: Granulocyte colony stimulating factor (G-CSF) products etc.

Rationale:

This is set in consideration of the safety of subjects and for the appropriate safety evaluation of DS-3032b.

5.8. Symptomatic Therapy

There are no regulations on symptomatic therapy in this study.

5.9. Management of Subjects

The investigator or subinvestigator will make efforts to maximize the subject's safety throughout the study period. Subjects must be hospitalized during the DLT evaluation period (refer to "Section 5.3.1 Definition of Dose-limiting Toxicities"). The investigator or subinvestigator may allow subjects to temporarily stay out overnight if it is considered feasible after carefully examining the subjects during hospitalization. If a subject stays out overnight, the study center will provide the subject with an instruction beforehand on how to communicate in an emergency.

If an AE occurs during hospitalization and the event is not confirmed to have resolved or be resolving before the scheduled day of hospital discharge, the investigator or subinvestigator will decide whether to continue hospitalization or not, taking the subject's safety into consideration.

6. STUDY PROCEDURES

6.1. List of Study Procedures

Study procedures specified in the protocol are shown in "Appendix 1."

In the study, the period from the day of informed consent through the end day of the Follow-up is defined as the "study period" for each subject. However, if follow-up of a subject at the study center becomes difficult for such reasons as transfer to another hospital or that the subject refuses to visit the site after the last dose of DS-3032b then the study duration for the pertinent subject will be terminated on the relevant day.

6.2. Study Procedures before Registration of Subjects

The following examinations and assessments, etc. will be performed and the results will be recorded in the case report form.

Data collected before informed consent can also be used if they are obtained within the acceptable limit for each item.

If the study treatment is started on Day 8 or later based on the day of registration defined as Day 0, the patient's eligibility should be assessed again on the preceding day or the start day (before administration) of study treatment.

1. Items confirmed after informed consent obtainment but before the start of subject registration

    - Date of informed consent to participate in this study
    - Subject identification code
    - Date of birth
    - Sex
    - Race
    - Height
    - Eligibility
    - Medical history and complications

      Symptoms that are expressed at the time of informed consent will be recorded as complications.

      Regarding medical history, only symptoms/diseases that were cured at the time of informed consent and are considered necessary to be reported at the investigator's or subinvestigator's discretion will be recorded.

    - Information on the underlying disease (AML)

      Collect data on the date of the first diagnosis, the World Health Organization (WHO) classification, and the date of relapse.

- Prior therapy

  The following items will be confirmed:

  - Medications for AML: Drug name, stop date, best response, number of courses
  - Radiation therapy for AML: Purpose, location, stop date, best response
  - Hematopoietic stem cell transplantation: Details, date of transplantation
  - Others: Details, stop date

- Assessment of SAEs

  Information on SAEs that occur from after informed consent to before the first dose of the study drug will be collected. Information on non-SAEs is not subject to collection during this period.

2. Items performed within 14 days before the day of registration (screening tests)
   *Performed on a day as close as possible to the day of registration

   - Vital sign measurement

     Axillary body temperature, pulse rate, and systolic and diastolic blood pressure will be measured at rest.

   - Body weight measurement
   - ECOG PS assessment

     Subject's general condition will be assessed in accordance with the criteria provided in "Appendix 2."

   - 12-lead ECG measurement (including evaluation of QTcF)

     A 12-lead ECG will be performed in the supine position after a 10-minute rest. Each measurement will be performed in triplicate at approximately 1- to 5-minute intervals.

   - Laboratory tests

	Laboratory Parameters
Hematology test	Red blood cell count, reticulocyte ratio, hemoglobin, hematocrit, white blood cell count, white blood cell differential count (neutrophils, basophils, eosinophils, lymphocytes, monocytes), platelet count, PT-INR, and aPTT
Blood chemistry test	Total protein, albumin, total bilirubin, direct bilirubin, AST, ALT, ALP, BUN, serum creatinine, uric acid, glucose, electrolytes (K, Na, Cl, Ca, P, Mg), and CRP
Urinalysis	Occult blood, glucose, and protein

- Assessment of bone marrow findings

  Assessment will be made based on bone marrow findings and peripheral blood results (neutrophil count, platelet count, and number of blasts) in accordance with "Section 10.1 Definition of Efficacy Endpoints."

  It is desired to obtain bone marrow specimens by bone marrow aspiration and biopsy. If the investigator or subinvestigator considers that the antitumor effect of DS-3032b can be assessed adequately using specimens obtained by bone marrow aspiration only, bone marrow biopsy may be skipped.

- Pregnancy test

  A urine or serum pregnancy test will be performed in female subjects.

  A pregnancy test is not necessary in women who have been amenorrheic for at least 12 months after the last menstruation and who are considered to have no childbearing potential, or women who are not of childbearing potential after permanent surgical sterilization, etc. In this case, the information and reason will be recorded in the case report form.

  A pregnancy test must be performed in women who have been amenorrheic for at least 12 months for medical reasons other than surgical sterilization (eg, medication) because they are considered to have childbearing potential.

3. Items confirmed within 90 days before the day of registration
   - HBs antigen, HBs antibody, HBc antibody, HBV-DNA level, HCV antibody, HIV antibody

6.3. Procedures During the Study Conduct Phase

The following examinations and assessments, etc. will be performed and the results will be recorded in the case report form. The details of the procedures are the same as those described in "Section 6.2 Study Procedures before Registration of Subjects."

6.3.1. Subtrial A (14/28 Day Schedule)

1. Confirmation of treatment compliance
   - Whether to have taken the drug or not
   - Date of administration
   - Time of administration
   - Dose (mg/day)
   - Whether or not the study treatment was interrupted or postponed, or the dose was reduced, and if there was any intervention, the details and reason.

2. Vital signs measurement

When screening tests are performed within 24 hours before the first dose of the study drug, the tests before administration on Day 1 of Cycle 1 are not necessary.

Cycle 1	Day 1 * Day of the first dose of the study drug	Pre-dose and 3 h post-dose (±10 min)
	Day 2	Pre-dose
	Day 8 (±2 days)	Pre-dose
	Day 14	Pre-dose and 3 h post-dose (±10 min)
	Day 22 (±2 days)	Specified day
Cycle 2	Day 1	Pre-dose
	Day 14 (−4 days)	Pre-dose
Cycle 3 and thereafter	Day 1 (−4 days)	Pre-dose

3. Body weight measurement, ECOG PS assessment

When screening tests are performed within 24 hours before the first dose of the study drug, the tests before administration on Day 1 of Cycle 1 are not necessary.

Cycle 1	Day 1 * Day of the first dose of the study drug	Pre-dose
	Day 8 (±2 days)	Pre-dose
	Day 14	Pre-dose
	Day 22 (±2 days)	Specified day
Cycle 2	Day 1	Pre-dose
	Day 14 (−4 days)	Pre-dose
Cycle 3 and thereafter	Day 1 (−4 days)	Pre-dose

4. 12-lead ECG

Cycle 1	Day 1 * Day of the first dose of the study drug	Pre-dose and 3 h post-dose (±10 min)
	Day 2	Pre-dose
	Day 8 (±2 days)	Pre-dose
	Day 14	Pre-dose and 3 h post-dose (±10 min)
	Day 22 (±2 days)	Specified day
Cycle 2	Day 1	Pre-dose
	Day 14 (−4 days)	Pre-dose
Cycle 3 and thereafter	Day 1 (−4 days)	Pre-dose

5. Laboratory tests

For clinical laboratory parameters, the reference rage of the institution that performs the measurements will be used. When screening tests are performed within 24 hours before the first dose of the study drug, the tests before administration on Day 1 of Cycle 1 are not necessary.

Cycle 1	Day 1 * Day of the first dose of the study drug	Pre-dose
	Day 2	Pre-dose
	Day 8 (±2 days)	Pre-dose
	Day 14	Pre-dose
	Day 22 (±2 days)	Specified day
Cycle 2	Day 1	Pre-dose
	Day 14 (−4 days)	Pre-dose
Cycle 3 and thereafter	Day 1 (−4 days)	Pre-dose

6. Pregnancy test

A urine or serum pregnancy test will be performed in female subjects.

A pregnancy test is not necessary in women who have been amenorrheic for at least 12 months after the last menstruation and who are considered to have no childbearing potential, or women who are not of childbearing potential after permanent surgical sterilization, etc. In this case, the information and reason will be recorded in the case report form.

A pregnancy test must be performed in women who have been amenorrheic for at least 12 months for medical reasons other than surgical sterilization (eg, medication) because they are considered to have childbearing potential.

Cycle 3	Day 1 (−4 days)	Pre-dose

7. Evaluation method of the antitumor effect

   Assessment will be made based on bone marrow findings and peripheral blood results (neutrophil count, platelet count, and number of blasts) in accordance with "Section 10.1 Definition of Efficacy Endpoints."

   It is desired to obtain bone marrow specimens by bone marrow aspiration and biopsy. If the investigator or subinvestigator considers that the antitumor effect of DS-3032b can be assessed adequately using specimens obtained by bone marrow aspiration only, bone marrow biopsy may be skipped.

Cycle 2 and thereafter	Day 25 of the previous cycle to pre-dose on Day 1 of the present cycle * After CR is achieved, assessment based on bone marrow findings may be skipped until blasts are observed in the peripheral blood.

8. Confirmation of concomitant drugs and therapies

   - Concomitant drugs and therapies

     The following information on concomitant drugs and therapies other than the study drug, which are used during the period from the day of the first dose of the study drug to the visit day of the Follow-up period will be confirmed. As for concomitant drugs or therapies that are newly started after the following day of the last dose of the study drug, those used only for the treatment of AEs will be confirmed as to the following information.

     - Name of drug (therapy), dose, unit, mode of administration, and dosage
     - Start and end dates of drug (therapy)
     - Reason for use (application)

     The following items need not to be recorded in the case report form, except when a relationship between the AEs occurring in subjects during their participation in the study and the study drug cannot be ruled out:

     - Antiseptic solutions

- Heparin for heparin lock flush
- Test drugs or treatment drugs used for tests including bone marrow aspiration or biopsy

- Transfusion

  The following information on transfusion that is introduced during the period from the day of the first dose of the study drug to the visit day of the Follow-up period will be confirmed. As for transfusion that is newly started after the following day of the last dose of the study drug, only cases of use for the treatment of AEs will be confirmed for the following information.

  - Type of blood products (whole blood, red blood cells, plasma, platelets, others)
  - Start date, end date, amount of use (unit)
  - Reason for use

9. Assessment of AEs

10. Collection of specimens for pharmacokinetic assessment and the biomarker study

    Refer to "Section 6.7 Pharmacokinetics" and "Section 6.8 Biomarker Study"

6.3.2. Subtrial B (7/28 Day Schedule)

1. Confirmation of treatment compliance
   - Whether to have taken the drug or not
   - Date of administration
   - Time of administration
   - Dose (mg/day)
   - Whether or not the study treatment was interrupted or postponed, or the dose was reduced, and if there was any intervention, the details and reason.

2. Vital signs measurement

When screening tests are performed within 24 hours before the first dose of the study drug, the tests before administration on Day 1 of Cycle 1 are not necessary.

Cycle 1	Day 1 * Day of the first dose of the study drug	Pre-dose and 3 h post-dose (±10 min)
	Day 2	Pre-dose
	Day 7	Pre-dose and 3 h post-dose (±10 min)
	Day 15 (±2 days)	Specified day
	Day 22 (±2 days)	Specified day
Cycle 2	Day 1	Pre-dose
	Day 7 (−2 days)	Pre-dose
	Day 22 (±2 days)	Specified day
Cycle 3 and thereafter	Day 1 (−4 days)	Pre-dose

3. Body weight measurement, ECOG PS assessment

When screening tests are performed within 24 hours before the first dose of the study drug, the tests before administration on Day 1 of Cycle 1 are not necessary.

Cycle 1	Day 1 * Day of the first dose of the study drug	Pre-dose
	Day 7	Pre-dose
	Day 15 (±2 days)	Specified day
	Day 22 (±2 days)	Specified day
Cycle 2	Day 1	Pre-dose
	Day 7 (−2 days)	Pre-dose
	Day 22 (±2 days)	Specified day
Cycle 3 and thereafter	Day 1 (−4 days)	Pre-dose

4. 12-lead ECG measurement

Cycle 1	Day 1 * Day of the first dose of the study drug	Pre-dose and 3 h post-dose (±10 min)
	Day 2	Pre-dose
	Day 7	Pre-dose and 3 h post-dose (±10 min)
	Day 15 (±2 days)	Specified day
	Day 22 (±2 days)	Specified day
Cycle 2	Day 1	Pre-dose
	Day 7 (−2 days)	Pre-dose
	Day 22 (±2 days)	Specified day
Cycle 3 and thereafter	Day 1 (−4 days)	Pre-dose

5. Laboratory tests

For clinical laboratory parameters, the reference rage of the institution that performs the measurements will be used. When screening tests are performed within 24 hours before the first dose of the study drug, the tests before administration on Day 1 of Cycle 1 are not necessary.

Cycle 1	Day 1 * Day of the first dose of the study drug	Pre-dose
	Day 2	Pre-dose
	Day 7	Pre-dose
	Day 15 (±2 days)	Specified day
	Day 22 (±2 days)	Specified day
Cycle 2	Day 1	Pre-dose
	Day 7 (−2 days)	Pre-dose
	Day 22 (±2 days)	Specified day
Cycle 3 and thereafter	Day 1 (−4 days)	Pre-dose

6. Pregnancy test

   A urine or serum pregnancy test will be performed in female subjects.

   A pregnancy test is not necessary in women who have been amenorrheic for at least 12 months after the last menstruation and who are considered to have no childbearing potential, or women who are not of childbearing potential after permanent surgical sterilization, etc. In this case, the information and reason will be recorded in the case report form.

   A pregnancy test must be performed in women who have been amenorrheic for at least 12 months for medical reasons other than surgical sterilization (eg, medication) because they are considered to have childbearing potential.

Cycle 3	Day 1 (−4 days)	Pre-dose

7. Evaluation method of the antitumor effect

   Assessment will be made based on bone marrow findings and peripheral blood results (neutrophil count, platelet count, and number of blasts) in accordance with "Section 10.1 Definition of Efficacy Endpoints."

   It is desired to obtain bone marrow specimens by bone marrow aspiration and biopsy. If the investigator or subinvestigator considers that the antitumor effect of DS-3032b can be assessed adequately using specimens obtained by bone marrow aspiration only, bone marrow biopsy may be skipped.

Cycle 2 and thereafter	Day 25 of the previous cycle to pre-dose on Day 1 of the present cycle * After CR is achieved, assessment based on bone marrow findings may be skipped until blasts are observed in the peripheral blood.

8. Confirmation of concomitant drugs and therapies

   - Concomitant drugs and therapies

     The following information on concomitant drugs and therapies other than the study drug, which are used during the period from the day of the first dose of the study drug to the visit day of the Follow-up period will be confirmed. As for concomitant drugs or therapies that are newly started after the following day of the last dose of the study drug, those used only for the treatment of AEs will be confirmed as to the following information.

     - Name of drug (therapy), dose, unit, mode of administration, and dosage
     - Start and end dates of drug (therapy)
     - Reason for use (application)

The following items need not to be recorded in the case report form, except when a relationship between the AEs occurring in subjects during their participation in the study and the study drug cannot be ruled out:

- Antiseptic solutions
- Heparin for heparin lock flush
- Test drugs or treatment drugs used for tests including bone marrow aspiration or biopsy

- Transfusion

  The following information on transfusion that is introduced during the period from the day of the first dose of the study drug to the visit day of the Follow-up period will be confirmed. As for transfusion that is newly started after the following day of the last dose of the study drug, only cases of use for the treatment of AEs will be confirmed for the following information.

  - Type of blood products (whole blood, red blood cells, plasma, platelets, others)
  - Start date, end date, amount of use (unit)
  - Reason for use

9. Assessment of AEs

10. Collection of specimens for pharmacokinetic assessment and the biomarker study

    Refer to "Section 6.7 Pharmacokinetics" and "Section 6.8 Biomarker Study"

6.3.3. Subtrial C (3/14 Day × 2 Schedule)

1. Confirmation of treatment compliance
   - Whether to have taken the drug or not
   - Date of administration
   - Time of administration
   - Dose (mg/day)
   - Whether or not the study treatment was interrupted or postponed, or the dose was reduced, and if there was any intervention, the details and reason.

2. Vital signs measurement

   When screening tests are performed within 24 hours before the first dose of the study drug, the tests before administration on Day 1 of Cycle 1 are not necessary.

Cycle 1	Day 1 * Day of the first dose of the study drug	Pre-dose and 3 h post-dose (±10 min)
	Day 3	Pre-dose and 3 h post-dose (±10 min)
	Day 8 (±2 days)	Specified day
	Day 15	Pre-dose and 3 h post-dose (±10 min)
	Day 17	Pre-dose and 3 h post-dose (±10 min)
	Day 22 (±2 days)	Specified day
Cycle 2	Day 1	Pre-dose
	Day 3	Pre-dose
	Day 15	Pre-dose
	Day 17	Pre-dose
Cycle 3 and thereafter	Day 1 (−4 days)	Pre-dose

3. Body weight measurement, ECOG PS assessment

   When screening tests are performed within 24 hours before the first dose of the study drug, the tests before administration on Day 1 of Cycle 1 are not necessary.

Cycle 1	Day 1 * Day of the first dose of the study drug	Pre-dose
	Day 3	Pre-dose
	Day 8 (±2 days)	Specified day
	Day 15	Pre-dose
	Day 17	Pre-dose
	Day 22 (±2 days)	Specified day
Cycle 2	Day 1	Pre-dose
	Day 3	Pre-dose
	Day 15	Pre-dose
	Day 17	Pre-dose
Cycle 3 and thereafter	Day 1 (−4 days)	Pre-dose

4. 12-lead ECG measurement

Cycle 1	Day 1 * Day of the first dose of the study drug	Pre-dose and 3 h post-dose (±10 min)
	Day 3	Pre-dose and 3 h post-dose (±10 min)
	Day 8 (±2 days)	Specified day
	Day 15	Pre-dose and 3 h post-dose (±10 min)
	Day 17	Pre-dose and 3 h post-dose (±10 min)
	Day 22 (±2 days)	Specified day
Cycle 2	Day 1	Pre-dose
	Day 3	Pre-dose
	Day 15	Pre-dose
	Day 17	Pre-dose
Cycle 3 and thereafter	Day 1 (−4 days)	Pre-dose

5. Laboratory tests

For clinical laboratory parameters, the reference rage of the institution that performs the measurements will be used. When screening tests are performed within 24 hours before the first dose of the study drug, the tests before administration on Day 1 of Cycle 1 are not necessary.

Cycle 1	Day 1 * Day of the first dose of the study drug	Pre-dose
	Day 3	Pre-dose
	Day 8 (±2 days)	Specified day
	Day 15	Pre-dose
	Day 17	Pre-dose
	Day 22 (±2 days)	Specified day
Cycle 2	Day 1	Pre-dose
	Day 3	Pre-dose
	Day 15	Pre-dose
	Day 17	Pre-dose
Cycle 3 and thereafter	Day 1 (−4 days)	Pre-dose

6. Pregnancy test

   A urine or serum pregnancy test will be performed in female subjects.

   A pregnancy test is not necessary in women who have been amenorrheic for at least 12 months after the last menstruation and who are considered to have no childbearing potential, or women who are not of childbearing potential after permanent surgical sterilization, etc. In this case, the information and reason will be recorded in the case report form.

   A pregnancy test must be performed in women who have been amenorrheic for at least 12 months for medical reasons other than surgical sterilization (eg, medication) because they are considered to have childbearing potential.

Cycle 3	Day 1 (−4 days)	Pre-dose

7. Evaluation method of the antitumor effect

   Assessment will be made based on bone marrow findings and peripheral blood results (neutrophil count, platelet count, and number of blasts) in accordance with "Section 10.1 Definition of Efficacy Endpoints."

   It is desired to obtain bone marrow specimens by bone marrow aspiration and biopsy. If the investigator or subinvestigator considers that the antitumor effect of DS-3032b can be assessed adequately using specimens obtained by bone marrow aspiration only, bone marrow biopsy may be skipped.

Cycle 2	Day 25 of the previous cycle to pre-dose on Day 1 of the present cycle * After CR is achieved, assessment based on bone marrow findings may be skipped until blasts are observed in the peripheral blood.

8. Confirmation of concomitant drugs and therapies

- Concomitant drugs and therapies

  The following information on concomitant drugs and therapies other than the study drug, which are used during the period from the day of the first dose of the study drug to the visit day of the Follow-up period will be confirmed. As for concomitant drugs or therapies that are newly started after the following day of the last dose of the study drug, those used only for the treatment of AEs will be confirmed as to the following information.

  - Name of drug (therapy), dose, unit, mode of administration, and dosage
  - Start and end dates of drug (therapy)
  - Reason for use (application)

  The following items need not to be recorded in the case report form, except when a relationship between the AEs occurring in subjects during their participation in the study and the study drug cannot be ruled out:

  - Antiseptic solutions
  - Heparin for heparin lock flush
  - Test drugs or treatment drugs used for tests including bone marrow aspiration or biopsy

- Transfusion

  The following information on transfusion that is introduced during the period from the day of the first dose of the study drug to the visit day of the Follow-up period will be confirmed. As for transfusion that is newly started after the following day of the last dose of the study drug, only cases of use for the treatment of AEs will be confirmed for the following information.

  - Type of blood products (whole blood, red blood cells, plasma, platelets, others)
  - Start date, end date, amount of use (unit)
  - Reason for use

9. Assessment of AEs

10. Collection of specimens for pharmacokinetic assessment and the biomarker study

    Refer to "Section 6.7 Pharmacokinetics" and "Section 6.8 Biomarker Study"

6.3.4. Subtrial D (21/28 Day Schedule)

1. Confirmation of treatment compliance
    - Whether to have taken the drug or not
    - Date of administration
    - Time of administration
    - Dose (mg/day)
    - Whether or not the study treatment was interrupted or postponed, or the dose was reduced, and if there was any intervention, the details and reason.

2. Vital signs measurement

    When screening tests are performed within 24 hours before the first dose of the study drug, the tests before administration on Day 1 of Cycle 1 are not necessary.

Cycle 1	Day 1 * Day of the first dose of the study drug	Pre-dose and 3 h post-dose (±10 min)
	Day 2	Pre-dose
	Day 8 (±2 days)	Pre-dose
	Day 15	Pre-dose
	Day 21	Pre-dose and 3 h post-dose (±10 min)
Cycle 2	Day 1	Pre-dose
	Day 15 (±2 days)	Pre-dose
	Day 21 (−2 days)	Pre-dose
Cycle 3 and thereafter	Day 1 (−4 days)	Pre-dose

3. Body weight measurement, ECOG PS assessment

When screening tests are performed within 24 hours before the first dose of the study drug, the tests before administration on Day 1 of Cycle 1 are not necessary.

Cycle 1	Day 1 * Day of the first dose of the study drug	Pre-dose
	Day 8 (±2 days)	Pre-dose
	Day 15	Pre-dose
	Day 21	Pre-dose
Cycle 2	Day 1	Pre-dose
	Day 15 (±2 days)	Pre-dose
	Day 21 (−2 days)	Pre-dose
Cycle 3 and thereafter	Day 1 (−4 days)	Pre-dose

4. 12-lead ECG measurement

Cycle 1	Day 1 * Day of the first dose of the study drug	Pre-dose and 3 h post-dose (±10 min)
	Day 2	Pre-dose
	Day 8 (±2 days)	Pre-dose
	Day 15	Pre-dose
	Day 21	Pre-dose and 3 h post-dose (±10 min)
Cycle 2	Day 1	Pre-dose
	Day 15 (±2 days)	Pre-dose
	Day 21 (−2 days)	Pre-dose
Cycle 3 and thereafter	Day 1 (−4 days)	Pre-dose

5. Laboratory tests

For clinical laboratory parameters, the reference rage of the institution that performs the measurements will be used. When screening tests are performed

within 24 hours before the first dose of the study drug, the tests before administration on Day 1 of Cycle 1 are not necessary.

Cycle 1	Day 1 * Day of the first dose of the study drug	Pre-dose
	Day 2	Pre-dose
	Day 8 (±2 days)	Pre-dose
	Day 15	Pre-dose
	Day 21	Pre-dose
Cycle 2	Day 1	Pre-dose
	Day 15 (±2 days)	Pre-dose
	Day 21 (−2 days)	Pre-dose
Cycle 3 and thereafter	Day 1 (−4 days)	Pre-dose

6. Pregnancy test

   A urine or serum pregnancy test will be performed in female subjects.

   A pregnancy test is not necessary in women who have been amenorrheic for at least 12 months after the last menstruation and who are considered to have no childbearing potential, or women who are not of childbearing potential after permanent surgical sterilization, etc. In this case, the information and reason will be recorded in the case report form.

   A pregnancy test must be performed in women who have been amenorrheic for at least 12 months for medical reasons other than surgical sterilization (eg, medication) because they are considered to have childbearing potential.

Cycle 3	Day 1 (−4 days)	Pre-dose

7. Evaluation method of the antitumor effect

   Assessment will be made based on bone marrow findings and peripheral blood results (neutrophil count, platelet count, and number of blasts) in accordance with "Section 10.1 Definition of Efficacy Endpoints."

   It is desired to obtain bone marrow specimens by bone marrow aspiration and biopsy. If the investigator or subinvestigator considers that the antitumor effect of DS-3032b can be assessed adequately using specimens obtained by bone marrow aspiration only, bone marrow biopsy may be skipped.

Cycle 2 and thereafter	Day 25 of the previous cycle to pre-dose on Day 1 of the present cycle * After CR is achieved, assessment based on bone marrow findings may be skipped until blasts are observed in the peripheral blood.

8. Confirmation of concomitant drugs and therapies

- Concomitant drugs and therapies

  The following information on concomitant drugs and therapies other than the study drug, which are used during the period from the day of the first dose of the study drug to the visit day of the Follow-up period will be confirmed. As for concomitant drugs or therapies that are newly started after the following day of the last dose of the study drug, those used only for the treatment of AEs will be confirmed as to the following information.

  - Name of drug (therapy), dose, unit, mode of administration, and dosage
  - Start and end dates of drug (therapy)
  - Reason for use (application)
- The following items need not to be recorded in the case report form, except when a relationship between the AEs occurring in subjects during their participation in the study and the study drug cannot be ruled out:
  - Antiseptic solutions
  - Heparin for heparin lock flush
  - Test drugs or treatment drugs used for tests including bone marrow aspiration or biopsy

- Transfusion

  The following information on transfusion that is introduced during the period from the day of the first dose of the study drug to the visit day of the Follow-up period will be confirmed. As for transfusion that is newly started after the following day of the last dose of the study drug, only cases of use for the treatment of AEs will be confirmed for the following information.

  - Type of blood products (whole blood, red blood cells, plasma, platelets, others)
  - Start date, end date, amount of use (unit)
  - Reason for use

9. Assessment of AEs

10. Collection of specimens for pharmacokinetic assessment and the biomarker study

    Refer to "Section 6.7 Pharmacokinetics" and "Section 6.8 Biomarker Study"

6.4. Procedures at Study Discontinuation

The investigator or subinvestigator will perform the following examinations and assessments, etc. on the day when discontinuation of the study is determined (±3 days).

If the study is discontinued after 25 days from the last dose of the study drug with the day of the last dose set as 0 for any reason, examinations and assessments, etc. specified in this section will be omitted, and examinations and assessments, etc. presented in "Section 6.5 Examination Items during the Follow-up Period and the Time Points" will be performed immediately instead.

The details of the procedures are the same as those described in "Section 6.2 Study Procedures before Registration of Subjects" and "Section 6.3 Procedures During the Study Conduct Phase."

- Date of discontinuation of the study and reason for discontinuation
- Vital signs measurement
- Body weight measurement
- ECOG PS assessment
- 12-lead ECG measurement
- Laboratory tests
- Assessment of bone marrow findings (It is desired to obtain bone marrow specimens by bone marrow aspiration and biopsy. If the investigators consider that the antitumor effect of DS-3032b can be assessed adequately using specimens obtained by bone marrow aspiration only, bone marrow biopsy may be skipped.)
- Confirmation of concomitant drugs and therapies
- Assessment of AEs
- Collection of biomarker specimens (blood and bone marrow)

6.5. Examination Items during the Follow-up Period and the Time Points

The following examinations and assessments, etc. will be performed after 30 days (±5 days) from the last dose of the study drug with the day of the last dose set as 0. If a subsequent AML treatment is introduced, Follow-up will be performed before the start of the subsequent AML treatment.

The end day of the Follow-up period is the day when all examinations and assessments, etc. are completed.

If any AE is persistent on the end day of the Follow-up period, follow-up investigation will be performed until the AE is confirmed to have resolved or be resolving as far as possible.

- Confirmation of survival (the last date of confirming survival) or death (the date of death)
- Vital signs measurement
- Body weight measurement
- ECOG PS assessment
- 12-lead ECG measurement
- Laboratory tests
- Confirmation of concomitant drugs and therapies
- Assessment of AEs
- Subsequent AML treatment after discontinuation of treatment with DS-3032b
- AML relapsed or not, if relapsed, the date of relapse
- [If the assessment at withdrawal is omitted (if the study is discontinued after 25 days from the last dose of the study drug with the day of the last dose set as 0 for any reason)] Assessment of bone marrow findings (It is desired to obtain bone marrow specimens by bone marrow aspiration and biopsy. If the investigators consider that the antitumor effect of DS-3032b can be assessed adequately using specimens obtained by bone marrow aspiration only, bone marrow biopsy may be skipped.)
- [If the assessment at withdrawal is omitted (if the study is discontinued after 25 days from the last dose of the study drug with the day of the last dose set as 0 for any reason)] Collection of biomarker specimens (blood and bone marrow)

6.6. Subsequent AML treatment

"Subsequent AML treatment" is defined as treatment introduced for the AML after the day of the last dose of the study drug, including HSCT, chemotherapy, immunotherapy, radiation therapy, and surgery, etc.

Subsequent AML treatment should not be initiated before the end day of the Follow-up period in this study as far as possible. If a subsequent AML treatment is introduced before the end of the Follow-up period for an unavoidable reason, the content of the subsequent AML treatment and the start date will be recorded in the case report form.

6.7. Pharmacokinetics

Plasma specimen will be obtained using a blood collection tube provided by the sponsor according to "Table 6.7.1 Blood Collection Points for Pharmacokinetic Assessment." The plasma specimens will be stored in a frozen state and be sent to the central laboratory

contracted by the sponsor. The details will be specified in separate procedures. Residual specimens collected in accordance with the procedures related to this study may be archived for a maximum of 15 years with the patient's consent for future biomarker assessment.

The time of each dosing and each blood collection will be recorded in the case report form.

Table 6.7.1: Blood Collection Points for Pharmacokinetic Assessment

Subtrial A (14/28 Day Schedule)

Treatment Cycle	Treatment Day	Blood Collection Point (Acceptable Time Window)
Cycle 1	Day 1	Pre-dose 1 h post-dose (±10 min) 2 h post-dose (±10 min) 3 h post-dose (±10 min) 6 h post-dose (±10 min) 8 h post-dose (±10 min)
	Day 2	Pre-dose
	Day 8	Pre-dose
	Day 14	Pre-dose 1 h post-dose (±10 min) 2 h post-dose (±10 min) 3 h post-dose (±10 min) 6 h post-dose (±10 min) 8 h post-dose (±10 min)
Cycle 2	Day 1	Pre-dose 3 h post-dose (±10 min)

Subtrial B (7/28 Day Schedule)

Treatment Cycle	Treatment Day	Blood Collection Point (Acceptable Time Window)
Cycle 1	Day 1	Pre-dose 1 h post-dose (±10 min) 2 h post-dose (±10 min) 3 h post-dose (±10 min) 6 h post-dose (±10 min) 8 h post-dose (±10 min)
	Day 2	Pre-dose
	Day 7	Pre-dose 1 h post-dose (±10 min) 2 h post-dose (±10 min) 3 h post-dose (±10 min) 6 h post-dose (±10 min) 8 h post-dose (±10 min)
	Day 8	24 h post-dose (±15 min) of Day 7
Cycle 2	Day 1	Pre-dose 3 h post-dose (±10 min)

Subtrial C (3/14 × 2 Day Schedule)

Treatment Cycle	Treatment Day	Blood Collection Point (Acceptable Time Window)
Cycle 1	Day 1	Pre-dose 1 h post-dose (±10 min) 2 h post-dose (±10 min) 3 h post-dose (±10 min) 6 h post-dose (±10 min) 8 h post-dose (±10 min)
	Day 2	Pre-dose
	Day 3	Pre-dose 1 h post-dose (±10 min) 2 h post-dose (±10 min) 3 h post-dose (±10 min) 6 h post-dose (±10 min) 8 h post-dose (±10 min)
	Day 4	24 h post-dose (±15 min) of Day 3
	Day 15	Pre-dose
	Day 16	Pre-dose
	Day 17	Pre-dose
Cycle 2	Day 1	Pre-dose 3 h post-dose (±10 min)

Subtrial D (21/28 Day Schedule)

Treatment Cycle	Treatment Day	Blood Collection Point (Acceptable Time Window)
Cycle 1	Day 1	Pre-dose 1 h post-dose (±10 min) 2 h post-dose (±10 min) 3 h post-dose (±10 min) 6 h post-dose (±10 min) 8 h post-dose (±10 min)
	Day 2	Pre-dose
	Day 8	Pre-dose
	Day 15	Pre-dose 1 h post-dose (±10 min) 2 h post-dose (±10 min) 3 h post-dose (±10 min) 6 h post-dose (±10 min) 8 h post-dose (±10 min)
	Day 21	Pre-dose
Cycle 2	Day 1	Pre-dose 3 h post-dose (±10 min)

Rationale

The results of the preceding overseas Phase 1 study showed that the median Tmax of DS-3032a following single and multiple oral doses of DS-3032b at 90 mg to 160 mg was approximately 3 hours post-dose. Referring to "Clinical Pharmacokinetic Studies of Pharmaceuticals,[18]" the blood collection time points required for pharmacokinetic evaluation of DS-3032a in this study were determined to be one time point immediately before administration, one time point before Tmax, and two time points around Tmax. Three time points of 6 hours, 8 hours, and 24 hours post-dose were also set in the elimination phase. Furthermore, to assess the time when the pharmacokinetics of DS-3032a reaches a steady state, two time points, namely, before administration on Day 2 of Cycle 1 and before administration on Day 8 of Cycle 1, were also set.

6.8. Biomarker Study

The biomarker study will be conducted in subjects who provide written informed consent for this clinical study. In the clinical study, blood, bone marrow, and serum will be collected to explore biomarkers potentially related to the mechanism of efficacy of DS-3032b.

6.8.1. Handling of Specimens for Biomarker Study

6.8.1.1. Blood and Bone Marrow

Whether a mutation in the *TP53* gene is present or not will be confirmed using blood and bone marrow in this study. When the result becomes available, the Investigator and the subject will be immediately notified of the information. If a *TP53* mutation is detected after the start of study treatment, the treatment will be discontinued unless it can be beneficial to the subject.

Blood and bone marrow will be collected at screening tests (within 14 days before the day of registration) and at the time of withdrawal. If the assessment at withdrawal is omitted (if the study is discontinued after 25 days from the last dose of the study drug with the day of the last dose set as 0 for any reason), they will be collected at the Follow-up. The details for submission will be specified in a separate procedure.

6.8.1.2. Serum

Serum MIC-1 levels will be measured to assess the effect of DS-3032b on MIC-1 induction because MIC-1 in serum is considered to be a major pharmacodynamic parameter of DS-3032b. Blood will be collected in accordance with "Table 6.8.1 Serum Collection Points." Obtained serum specimens will be immediately stored frozen and the specimens will be submitted to the specimen collection agency contracted by the sponsor. The details will be specified in separate procedures.

Table 6.8.1: Serum Collection Points

Subtrial A (14/28 Day Schedule)

Cycle	Day	Blood Collection Point
Cycle 1	Day 1	Pre-dose
	Day 2	Pre-dose
	Day 8	Pre-dose
	Day 14	Pre-dose
	Day 22	Specified day
Cycle 2	Day 1	Pre-dose

Subtrial B (7/28 Day Schedule)

Cycle	Day	Blood Collection Point
Cycle 1	Day 1	Pre-dose
	Day 2	Pre-dose
	Day 7	Pre-dose
Cycle 2	Day 1	Pre-dose

Subtrial C (3/14 × 2 Day Schedule)

Cycle	Day	Blood Collection Point
Cycle 1	Day 1	Pre-dose
	Day 2	Pre-dose
	Day 3	Pre-dose
	Day 15	Pre-dose
	Day 16	Pre-dose
	Day 17	Pre-dose
Cycle 2	Day 1	Pre-dose

Subtrial D (21/28 Day Schedule)

Cycle	Day	Blood Collection Point
Cycle 1	Day 1	Pre-dose
	Day 2	Pre-dose
	Day 15	Pre-dose
	Day 21	Pre-dose
Cycle 2	Day 1	Pre-dose

6.8.2. Anonymization, Storage, and Disposal of Specimens for Biomarker Study

6.8.2.1. Anonymization of Specimens

The specimens to be submitted will be anonymized using subject identification codes to prevent subjects' personal information from being identified. The correspondence table between the subject identification codes and the subjects' personal information will be strictly stored at the study center, so that neither the sponsor, nor the specimen collection agency or the biomarker laboratory can identify a subjects' personal information. The sponsor will be able to link the results of the biomarker study with the subject identification code and the subjects' study data.

6.8.2.2. Storage of Specimens

In consideration of the possibility that the relationship between the efficacy or safety of DS-3032b and the biomarkers is additionally analyzed based on the newly obtained knowledge, the submitted specimens will be stored for a maximum of up to 15 years after the time of submission of the clinical trial plan notification.

6.8.2.3. Disposal of Specimens

At the expiration of the storage period, the biomarker laboratory will dispose of all specimens according to the sponsor's directions.

When a subject withdraws consent for the biomarker study, the specimens will be disposed of, depending on the location of the specimens at the time of the request, according to the procedure listed below. If biomarker analysis has already been performed by the biomarker laboratory at the time of the subject's withdrawal of consent, the data will not be destroyed.

1. In cases where the specimens are temporarily stored at the study center:

   The investigator or subinvestigator will identify the specimens of the subject and dispose of them.

2. In case the specimens are stored in the specimen collection agency:

   The investigator or subinvestigator will report the subject identification code of the pertinent subject to the sponsor. The sponsor will direct the agency to dispose of the specimens of the subject.

6.9. Long-term Storage (Banking) of Clinical Specimens for Genome/Gene Analysis

In preparation for future research to analyze the relationship between the pharmacokinetics, pharmacodynamics, and safety of DS-3032b and genomes and/or genes, specimens of DNA extracted from oral mucosa of subjects will be archived over a long period of time (banking) in accordance with the following procedures. The details of handling specimens will be specified separately in the "Procedure for Banking."

6.9.1. Specimens to be Banked

Subjects will be explained about banking as per procedure given in "Section 15.5 Informed Consent for Storage (Banking) of Specimens for Genome/Gene Analysis." Specimens obtained from subjects who have provided informed consent for banking will be banked. The investigator or subinvestigator will record the date of informed consent of subjects providing consent for specimen banking in the case report form. In subjects with a medical history, etc. that may affect genomic or genetic information (eg, allogenic bone marrow transplantation), the information should also be recorded in the case report form.

6.9.2. Collection of Oral Mucosa

Oral mucosa will be collected before the first dose of the study drug and stored frozen (−20°C or below) until transportation. The investigator or subinvestigator will record the date of collection in the case report form. The specimens should be managed by attaching a code unrelated to the subjects to avoid leaking of subjects' personal information.

6.9.3. Storage Period

The storage period of the banking specimens will be up to a maximum of 15 years after the day of submission of the clinical trial plan notification.

6.9.4. Disclosure of Results of Genome/Gene Analysis Using Banking Specimens

The timing, methods, accuracy of the results, and clinical significance of the genome/gene analysis using banked specimens remain unknown at present. In this context, disclosure of the results of genome/gene analysis to investigators and subjects is not planned.

6.9.5. Disposal of Banking Specimens

After the expiration of the storage period or at the time of a subject's withdrawal of consent during the storage period, the banking specimens will be disposed of without delay. If the gene analysis has been performed before the expiration of the storage period or before the subject's withdrawal of consent, the data will not be destroyed.

7. PHARMACOKINETIC ENDPOINTS

The pharmacokinetic parameters listed below will be calculated from plasma concentrations of DS-3032a using the non-compartmental analysis.

Pharmacokinetic parameters (Subtrial A):

C1D1 (Cycle 1 Day 1): Cmax, Tmax, AUClast, AUC8h, AUC24h, AUCinf*, Kel*, t1/2*, CL/F*, Vz/F*

C1D14 (Cycle 1 Day 14)**: Cmax, Ctrough, Cavg, Tmax, AUC8h, AUC24h, Kel*, t1/2*, CLss/F***, Vz/F*,***, AR

*: To be calculated only if possible.

**: To be read as C1D7 (Cycle 1 Day 7) in Subtrial B, C1D3 (Cycle 1 Day 3) in Subtrial C, and C1D15 (Day 15) in Subtrial D.

***: Not to be calculated because steady state will not be reached in Subtrial C.

The details of the method of calculation of pharmacokinetic parameters are specified in the Statistical Analysis Plan.

Rationale:

To evaluate the pharmacokinetics of DS-3032b administered as a single dose or multiple doses, general pharmacokinetic parameters after oral dosing are selected.

8. PHARMACODYNAMIC ENDPOINTS

The following pharmacodynamic parameters will be analyzed:

- *TP53* mutation
- Serum MIC-1 level

Rationale:

These pharmacodynamic parameters that can be drug-related markers will be measured to assess the pharmacological or clinical effect of DS-3032b in each individual.

9. SAFETY ENDPOINTS

Safety endpoints will be AEs, ECOG PS, laboratory data, body weight, vital signs, and 12-lead ECG.

9.1. Definition of Adverse Events

An AE is any untoward or unintended sign (including an abnormal change in laboratory data or vital signs), symptom, or disease noted in subjects who received the study drug, whether it is considered to be related to the study drug or not.

A symptom or disease preexisting before the start of study treatment will be handled as a complication, not as an AE. However, complications that have worsened during the study treatment will be handled as AEs, and the date when worsening is confirmed will be used as the date of onset of the relevant event.

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

Progression of the primary disease (AML) will be handled as follows:

- Tumor progression will not be considered as an AE. However, if tumor progression results in death during the AE collection period, it will be handled as an SAE (this should be recorded as “disease progression” for the event term and “fatal” for the outcome).
- Worsening of signs or symptoms resulting from tumor progression will be handled as AEs.

9.2. Definition of Serious Adverse Events

An SAE is any AE that:

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

SAEs that occurs after the informed consent will be collected.

9.3. Adverse Event Information to be Reported

If an AE occurs during the study, the items shown in "Table 9.3.1 Adverse Event Information to be Reported" will be investigated and recorded in the case report form. If a medical interview is used to investigate symptoms, questions that specify symptoms should not be used. If a subject has two or more signs (including symptoms and abnormal changes in laboratory data) that are correlated with each other and can be considered part of one diagnosis, they will be regarded as one single event, and the diagnosis will be recorded as an AE in the case report form. Only the highest grade observed in the course of each AE should be recorded as the severity in the case report form.

AEs will be graded according to the "CTCAE Version 5.0." AEs that are not listed in the CTCAE Version 5.0 will be graded according to the definitions provided in "Table 9.3.1 Adverse Event Information to be Reported."

Table 9.3.1: Adverse Event Information to be Reported

Item		Details to be Assessed	
AE		Name of AE, date of onset	
Action taken for AE		Whether or not action was taken (including the modification of administration of the study drug), and if taken, details of the action.	
Outcome		Outcome category, date of outcome assessment, date of resolution	
	Outcome category	Recovered/ Resolved	The AE has resolved, and the subject has recovered to the pre-event condition.
		Recovering/ Resolving	The AE has almost resolved, and the subject has nearly recovered to the pre-event condition.
		Not recovered/ Not resolved	The AE has not resolved, and the condition of the subject is similar to that at onset (unchanged).
		Recovered/ Resolved with sequelae/ residual effect(s) present	The AE has resolved, but the subject has sequelae.
		Fatal	Tumor progression will not be handled as an AE. However, tumor progression leading to a fatal outcome during the AE collection period should be handled as a SAE (with the name and outcome of the event recorded as "disease progression" and "fatal," respectively).
		Unknown	Outcome is unknown because of lack of information.
Severity		To be assessed according to the CTCAE Version 5.0. The severity of AEs not included in the CTCAE Version 5.0 will be assessed according to the following grades:	
		Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
		Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
		Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
		Grade 4	Life-threatening consequences; urgent intervention indicated.
		Grade 5	Death related to AE.
Seriousness		Serious/Nonserious	
Causality with the study drug		Classification of the relationship (in accordance with the following classification of the relationship), reason for the assessment	
	Causality category	Related	• There is a reasonable temporal relationship between the onset of the adverse event and administration of the study drug, it is not reasonable to assess that the adverse event is attributable to the subject's condition or other factors than the study drug (underlying disease, complications, concomitant drugs, etc.), and a relationship with the study drug cannot be ruled out. • There is a reasonable temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event can be explained by known actions or the pharmacological action of the study drug or similar analogues.
		Unrelated	• There is no reasonable temporal relationship between the onset of the AE and administration of the study drug, it is reasonable to assess that the AE is attributable to the subject's condition or other factors than the study drug (underlying disease, complications, concomitant drugs, etc.), and a relationship with the study drug can be ruled out.

9.4. Definition of Adverse Drug Reactions

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

9.5. Actions to be Taken for Adverse Events

9.5.1. Recommended Action for Adverse Events

If any adverse event has occurred, the investigator or subinvestigator will provide appropriate medication, notify the sponsor as required, and continue follow-up until the subject recovers to the pre-event condition with resolution or relief of the adverse event as far as possible, even after the end of this study. However, even if the adverse event is not confirmed to have resolved or relieved, if it is judged that the subject's condition remains stable and the safety can be assured, the investigator or subinvestigator will explain the matter to the subject, and the follow-up of the study will be completed (treatment of the relevant symptom will be continued).

9.5.2. Action for Serious Adverse Events

If an SAE has occurred, the investigator or subinvestigator will provide appropriate medication, and report the details of the SAE to the sponsor by telephone or fax within 24 hours of learning of the occurrence. The investigator will also record the necessary information in the "Serious Adverse Event Report (SAVER)" Form, sign it with the date of confirmation, and immediately report it to the sponsor. A written report to the head of the study center will be made in accordance with the procedures and format specified by the study center.

9.6. Actions to be Taken in the Event That Information on Pregnancy, Pregnant and Parturient Women, and Delivery is Obtained

If information on the pregnancy of a subject or a subject's female partner is obtained during the study period or within 95 days after the last dose of the study drug, the investigator or subinvestigator will investigate the information on the pregnancy through delivery, and report it to the sponsor using the format provided by the sponsor. Pregnancy will not be handled as an AE; however, if the outcome of the pregnant woman falls under the definition of SAEs (congenital anomaly in the fetus [including suspected cases], stillbirth, abortion, etc.), the investigator or subinvestigator must report it to the sponsor in accordance with the procedures for reporting SAEs specified in "Section 9.5.2 Action for Serious Adverse Events," independent of whether it is during the study period or not.

10. EFFICACY ENDPOINTS

The antitumor effect of DS-3032b will be evaluated based on bone marrow findings and peripheral blood results (neutrophil count, platelet count, and number of blasts), as specified in "Table 10.1.1 Definition of Efficacy Endpoints."

10.1. Definition of Efficacy Endpoints

The response criteria are defined as follows.

Table 10.1.1: Definition of Efficacy Endpoints

Complete remission: CR*	Bone marrow blasts <5%, neutrophil count ≥1000 /mm^3, and platelet count ≥100,000 /mm^3 in the absence of RBC or platelet transfusion (4 weeks for RBC transfusion, 1 week for platelet transfusion); absence of Auer rods; absence of extra-medullary leukemia. Absence of peripheral blasts.
CR with incomplete hematological recovery: CRi	All CR criteria are met, except for neutrophil count <1000 /mm^3 and platelet count ≥100,000 /mm^3 or neutrophil count ≥1000 /mm^3 and platelet count <100,000 /mm^3.
CR with partial hematological recovery: CRh**	All CR criteria are met, except for neutrophil count >500 /mm^3 and platelet count >50,000 /mm^3.
Partial remission: PR	Neutrophil count ≥1000 /mm^3 and platelet count ≥100,000 /mm^3 in the absence of RBC or platelet transfusion (4 weeks for RBC transfusion, 1 week for platelet transfusion); decrease in bone marrow blast percentage by at least 50% and total bone marrow blast percentage of 5% to 25%.
Morphologic leukemia-free state: MLFS	Bone marrow blasts <5% in the absence of blasts with Auer rods; absence of extra-medullary leukemia. The presence/absence of hematological recovery or blood transfusion is not considered.
Stable disease: SD	Absence of CR, CRi, CRh, PR, or MLFS; and criteria for PD not met.
Progressive disease: PD	When any of the following apply: >1.5-fold increase in bone marrow blasts over baseline (eg, increase in blast count from 35% to >52.5%). At least 15% point increase in bone marrow blasts in cases with <30% blasts at baseline (eg, increase in blast count from 20% to 35%). Persistent bone marrow blast percentage of >70% over at least 3 months. Cases with improvement in neutrophil count to ≥500 /mm^3 and/or improvement in platelet count to ≥50,000 /mm^3 (without transfusion) are excluded. >1.5-fold increase in peripheral blasts (WBC × % blasts) to >25,000 /mm^3, in the absence of differentiation syndrome. New extra-medullary leukemia.
Relapse	Relapse after CR, CRi, or CRh (except in case the criteria for MLFS are also met): Either of appearance of peripheral blasts, bone marrow blast percentage ≥5%, or relapsed or new extra-medullary leukemia.
Unknown	No post-baseline evaluation.

* If a subject meets the criteria for both CR and CRh, the outcome should be captured in the case report form as CR.
** If a subject meets the criteria for both CRi and CRh or for both CRh and MLFS, the outcome should be captured in the case report form as CRh.

10.2. Best Response

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

The best response will be SD if the response is assessed as SD three or more times consecutively in the protocol-specified evaluation of the antitumor effect. If the response is not assessed as SD three or more times consecutively, the best response will be Not Applicable (unconfirmed SD).

10.3. Duration of Composite Complete Remission

The duration of composite CR (CRc) is defined as the length of time from the time when the criteria for CRc (CR + CRi + CRh) are first met to the time when a relapse was first confirmed.

11. STATISTICAL ANALYSIS

An outline of the statistical and pharmacokinetic analyses is provided below. Statistical methods will be specified in more details in the separately prepared Statistical Analysis Plan.

11.1. General Statistical Considerations

Patients treated with the same dose level and schedule will be pooled into a single treatment group. All statistical analyses will be performed by treatment group, unless otherwise noted. Subjects whose dose is reduced will be analyzed in the dose group before dose reduction.

Baseline values of each subject, unless otherwise specified, will be the last observed values that are available before the first dose of the study drug.

Unless otherwise noted, continuous variables will be summarized by the number of subjects analyzed, arithmetic mean, standard deviation, minimum, median, and maximum, whereas categorical variables will be summarized by frequency and proportion. Analyses of changes from baseline (eg, absolute change, shift table) will be performed for subjects with the baseline value and at least one value available after treatment. Two-sided 95% confidence interval (CI) will be determined, unless otherwise noted.

11.2. Analysis Sets

The sponsor will define the criteria for inclusion of subjects in each analysis set in the Statistical Analysis Plan, and will determine whether each subject should be included or not according to the criteria. Subjects with major Good Clinical Practice (GCP) violations (eg, a violation of informed consent procedure, a major violation of study procedures) will be excluded from all analysis sets.

11.2.1. Safety Analysis Set

The safety analysis set will include subjects enrolled in the study but will exclude "subjects who have not received any dose of the study drug."

11.2.2. Maximum Tolerated Dose Analysis Set

The MTD analysis set will include all subjects who received at least one dose of the study drug but will exclude subjects who have missing data of one or more examination or observation items during the DLT evaluation period for other reasons than adverse drug reactions (worsening of clinical conditions due to progression of the primary disease, AEs for which a relationship with the study drug is ruled out, etc.) and whose DLT evaluation could not be performed appropriately. The MTD analysis set will also include subjects who have experienced DLT in Cycle 1 and subjects who have received the study drug on at least 75% of the specified days in Cycle 1 in the absence of DLT.

Subjects for whom the study treatment is postponed due to a DLT occurring during the DLT evaluation period, and the study treatment is then resumed at a reduced dose will be

handled as those included in the MTD analysis set for the dose level at the first dose of the study drug.

11.2.3. Efficacy Analysis Set

The efficacy analysis set will include all subjects who received at least one dose of the study drug and who underwent efficacy evaluation after administration at least once.

11.2.4. Pharmacokinetic Analysis Set

The pharmacokinetic analysis set will include subjects who received at least one dose of the study drug, whose specimens for pharmacokinetics have been collected at least once after the start of treatment, and who have available data of the measurement.

11.2.5. Biomarker Analysis Set

The biomarker analysis set will include subjects who received at least one dose of the study drug, whose specimens for biomarker research have been collected, and who have available data of the measurement.

11.3. Data Handling

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

11.4. Statistical Analysis Items and Methods

11.4.1. Baseline Subject Characteristics

For baseline subject characteristics (demographic variables and baseline values), distributions and summary statistics will be calculated. Frequency tables will be prepared for categorical data and summary statistics will be calculated for quantitative data. Analyses will be performed in the safety analysis set, MTD analysis set, efficacy analysis set, pharmacokinetic analysis set, and biomarker analysis set.

11.4.2. Safety Analysis

Safety will be analyzed in the safety analysis set, unless otherwise noted. AEs that occur or worsen relative to the pre-treatment state after the start of study treatment (TEAEs) will be tabulated. AE terms will be converted using the Medical Dictionary for Regulatory Activities (MedDRA) terminology developed by the ICH. Individual AEs will be grouped by organ system using the system organ classes (SOC) of MedDRA, and be summarized in the preferred term (PT) level.

11.4.2.1. Adverse Events

For TEAEs and TEAEs assessed as “related” to the study drug, frequency tables will be prepared as classified below. The grade of AEs will be assessed according to the CTCAE Version 5.0. In the tabulation by grade, only the highest-grade event in each subject will be counted for tabulation.

- Subjects with TEAEs (by grade; including events classified as Grade ≥3)
- Subjects with serious TEAEs
- Subjects who have interrupted study treatment because of a TEAE
- Subjects withdrawn from study treatment because of a TEAE

For TEAEs and TEAEs assessed as "related" to the study drug, frequency tables will be prepared by event as classified below. The grade of AEs will be assessed according to the CTCAE Version 5.0. If a subject reports a single event two or more times, only the highest-grade event will be counted for tabulation.

- TEAEs
- TEAEs by grade (including events classified as Grade ≤2 and Grade ≥3)
- Serious TEAEs
- TEAEs leading to interruption of study treatment
- TEAEs leading to discontinuation of study treatment

11.4.2.2. Dose-limiting Toxicity

Frequency table(s) with detailed descriptions of DLTs (if any) will be prepared.

11.4.2.3. Laboratory Data

For hematology and blood chemistry tests, summary statistics of measured values and changes from baseline will be calculated at each scheduled time point. For urinalysis (qualitative data), shift tables of measured values at baseline and those at each time point will be prepared. For urinalysis (quantitative data), summary statistics will be calculated at each time point.

11.4.2.4. Height, Body Weight, and Vital Signs (Blood Pressure, Pulse Rate, and Body Temperature)

For blood pressure (systolic and diastolic), pulse rate, body temperature, and body weight, summary statistics of measured values and changes from baseline will be calculated at each time point.

11.4.2.5. Electrocardiogram

In the 12-lead ECG analysis on PR, QRS, RR, and QT intervals, QT corrected for heart rate using Bazett's method (QTcB), QTcF, and heart rate, summary statistics of measured values and changes from baseline will be calculated at each time point. For QTcF, frequency tables will be prepared according to the following categories:

Absolute QTcF:

- QTcF >450 ms
- QTcF >480 ms
- QTcF >500 ms

Changes in QTcF from baseline:

- Increase in QTcF from baseline >30 ms
- Increase in QTcF from baseline >60 ms

11.4.3. Efficacy Analysis

The efficacy analyses will be performed on the efficacy analysis set, unless otherwise noted.

For the best response (CR, CRi, CRh, PR, MLFS, SD, and PD), frequency tables will be prepared. The point estimate and the 95% CI will be calculated for the CRc rate, response rate, and transplantation rate (as a subsequent AML treatment).

For the duration of CRc, summary statistics will be calculated using the Kaplan-Meier method.

11.4.4. Pharmacokinetic Analysis

Pharmacokinetics will be analyzed for each subtrial in the pharmacokinetic analysis set.

Summary statistics of plasma concentrations of DS-3032a will be calculated by dose at each time point, and a plasma concentration-time profile will be prepared.

For the pharmacokinetic parameters that are calculated by the non-compartmental analysis, summary statistics will be calculated by dose. The relationship between dose and each pharmacokinetic parameter will also be assessed.

11.4.5. Pharmacodynamic Analysis

For PDy values and PDy parameters, summary statistics will be calculated by treatment group. The time profile of PDy values will be prepared.

11.4.6. Other Analyses

Analyses using modeling and simulation, including population pharmacokinetic analysis and pharmacokinetic/pharmacodynamic analysis, will be performed using plasma DS-3032a concentration data, where appropriate. If the analyses are performed, the results will be separately reported.

11.5. Changes to the Analysis Plan

When it is considered necessary to change the analysis plan, the sponsor will discuss the appropriateness of the change and potential influences on evaluations in the study, and determine whether the change is feasible or not. The sponsor will clearly document and retain the content of the discussion about the change in the analysis plan, whether the change was made or not, and the reason for the change if it is made. The details of all changes in the analysis plan that have been made will be documented with the reasons in the clinical study report.

11.6. Planned Sample Size

9 to 24 subjects

Rationale:

In this study, DLT evaluation will be conducted in at least 3 subjects per cohort in principle, and the safety of DS-3032b at doses up to 160 mg will be confirmed in Subtrial A unless the completion criteria provided in "Section 5.3.2 Definition of Maximum Tolerated Dose" are met. If no DLT occurs in any of the cohorts before the 160 mg cohort, the total number of subjects in this study will be the minimum. In this case, a total number of 9 subjects, consisting of 3 subjects each in the 90 mg, 120 mg, and 160 mg cohorts, will participate in the study. For instance, if 6 subjects participate in each of the 90 mg, 120 mg, and 160 mg cohorts, the total number of subjects participating in the study will be 18. Also, if two or more dosing schedules are assessed, the total number of subjects may be further increased.

11.7. Details of Modified Continual Reassessment Method

The details of mCRM used for explorative dose finding in Subtrial A will be provided in this section, unless otherwise noted.

11.7.1. Bayesian Logistic Regression Model

The following BLRM will apply to the dose-response relationship for DLTs:

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

where $\text{logit}(\pi(d)) = \ln(\pi(d) / (1 - \pi(d)))$, $\pi(d)$ is the DLT rate at a dose of d, and d* is 160 mg. As a consequence, $\log(\alpha)$ is equal to $\text{logit}(\pi(d^*))$ at the dose of d*. Note that if the dose is zero, the DLT rate is also zero. If other dosing schedules are assessed, d* will be set separately based on the information obtained up to that time.

11.7.2. Prior Distribution of Bayesian Logistic Regression Model

Assuming that BLRM model parameters $\log(\alpha)$ and $\log(\beta)$ follow bivariate normal distribution, a minimally informative prior distribution is set as follows. If other dosing schedules are assessed, each parameter will be set separately based on the information obtained up to that time.

Parameter	Mean	Standard Deviation	Correlation Coefficient
$\log(\alpha)$, $\log(\beta)$	(−1.8999, 1.3484)	(2.2792, 1.3727)	−0.3157

The above parameters for a prior distribution will be calculated as shown below.

- Based on the overseas Phase 1 study (U102), the median probability of the DTL rate was estimated to be 5% and 20% for the 120 mg qd 21/28 day schedule and the 160 mg qd 21/28 day schedule, respectively.
- From the ratio (0.67) of the dosing days in this study to U102, the median probability of the DTL rate is assumed to be 3% and 13% at doses of 120 mg and 160 mg, respectively, in this study.
- Based on the median probability of the DTL rate at the above doses, parameters of the bivariate normal distribution will be calculated to generate vague prior Bayesian intervals (to minimize prior information) using minimal information beta distribution.

11.7.3. Recommended Dose for the Next Cohort by Bayesian Logistic Regression Model Incorporating the Escalation with Overdose Control Principle

The recommended dose in the next cohort is decided based on posterior distribution of the DLT rate at planned doses (90 mg, 120 mg, and 160 mg). After completing DLT evaluation in 3 subjects per cohort in principle, posterior distribution of the DLT rate at each planned dose will be estimated using BLRM based on the results of DLT evaluation and prior distribution set in "Section 11.7.2 Prior Distribution of Bayesian Logistic Regression Model," and posterior probability of the DLT rate falling under the following four intervals will then be calculated for each planned dose. The following posterior probabilities can also be calculated for other doses than the planned, as long as the dose is more than 1.3 times but not more than 2 times of the dose in the concerned cohort.

- [0, 16%]: DLT rate interval for under-dosing
- (16, 33%]: target DLT rate interval
- (33, 60%]: DLT rate interval for excessive toxicity
- (60, 100%]: DLT rate interval for unacceptable toxicity

Among the planned doses and additional candidate doses, the dose with posterior probability of 25% for the DLT rate exceeding 33% (probability for excessive and unacceptable toxicity) (according to the EWOC principle) and with the highest posterior probability for the DLT rate being more than 16% and 33% or less (probability for target DLT rate interval) will be chosen as the recommended dose for the next cohort. The EWOC principle will apply from the third cohort. Dose increments for the next cohort should be within the 1.3-fold and 2-fold range.

12. QUALITY CONTROL AND QUALITY ASSURANCE

The sponsor will implement the quality assurance and quality control system in accordance with the standard operating procedures specified by the sponsor to ensure that the implementation of the study and the generation, recording, and reporting of data are in compliance with the following:

1. The clinical study protocol
2. Standards stipulated in Article 14, Paragraph 3 and Article 80-2 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (hereinafter referred to as the PMD Act)
3. GCP ordinance

In addition, the sponsor will perform quality control at each stage of data handling to ensure the reliability and proper processing of all study-related data. The methods for quality control will be prepared in advance in accordance with the standard operating procedure specified by the sponsor, and the implementation will be recorded.

The sponsor's responsible auditor will perform GCP auditing as part of quality assurance operations to determine whether the study is conducted in compliance with GCP, the clinical study protocol, and the written procedures independently and separately from the regular monitoring and study quality control operations.

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

13.1. Payment for Participation

As compensation to reduce the subject's burden, etc., the study center will pay subjects an amount from the funds paid by the sponsor to the study center according to the separately specified regulations of the study center.

13.2. Compensation for Study-related Injuries

If a subject experiences any study-related injury resulting from participation in the study, the investigator or subinvestigator will take the necessary actions, including treatment. If the subject makes a claim for study-related injury, the sponsor will be promptly notified. The sponsor will specify the procedures for compensation for study-related injury resulting from participation in the study and take actions such as purchase of an insurance policy. In the event of any study-related injury occurring in a subject, the sponsor will bear the expenses that are paid by the subject for treatment of the injury, excluding the amount covered by health insurance, etc. For injuries that are as severe as requiring hospitalization, the sponsor will also pay a medical allowance based on the amount set in the Relief System for Sufferers from Adverse Drug Reactions. However, this will not apply to study-related injuries in case:

1. If there is clear evidence of any other cause of study-related injury.
2. If there is no reasonable temporal relationship between administration of the study drug and the occurrence of the study-related injury.
3. If a perpetrator has been identified (for instance, traffic accident).
4. If there were no therapeutic benefits because of lack of efficacy.
5. If a subject or a subject's partner is found to be pregnant during the study.
6. If there is any protocol violation without due reason.

If a study-related injury is caused by an intentional act or gross negligence on the part of the study center or the subject, compensation may not be paid or may be reduced.

13.3. Insurance

In case of compensation for study-related injury, the sponsor will purchase an insurance policy as required. In case of study-related injury due to medical malpractice, the study center will purchase an insurance policy and take other measures as required.

14. PUBLICATION POLICY

15. STUDY ADMINISTRATIVE INFORMATION

15.1. Ethics

15.1.1. Ethical Conduct of the Study

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

Genome/gene analysis to be performed during the study, banking of clinical specimens for the genome/gene analysis, and a research study using the specimens will be performed in accordance with "Ethical Guidelines for Human Genome/Gene Analysis Research[19]" and "Ethical Guidelines for Clinical Studies[20]" in addition to the above (only at the study centers that are granted approval for the conduct of genome/gene analysis or banking for genome/gene analysis).

15.1.2. Institutional Review Board

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

15.2. Subject Confidentiality

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

15.3. Procedures for Informed Consent

The investigator or subinvestigator will explain the details of the study listed below to subject candidates who have applied to participate in the study in a readily understandable way using the informed consent documents, before any screening tests are performed, and will obtain written informed consent to participate in the study from subjects on their free will. Before obtaining consent, the investigator or subinvestigator should give the subject ample time and opportunity to ask questions to decide whether to participate in the study, and should answer the questions to the satisfaction of the subject.

Identification of *TP53* mutation is not necessarily required before the first dose of the study drug; however, if the test result becomes available during the study, the Investigator and the subject will be immediately notified. If a *TP53* mutation is detected after the start of treatment, the treatment will be continued only when it is considered clinically meaningful.

The investigator or subinvestigator should adequately explain this matter to subjects and obtain written informed consent from the subjects based on their free will.

The investigator or subinvestigator who has provided an explanation and the subject who has given consent will sign and date the consent form. If study staff personnel have provided a supplementary explanation to the subject, the study staff should also sign and date the form. A copy of the consent form along with the subject information form will be provided to the subject, and the original consent form will be retained at the study center. The investigator or subinvestigator will document (eg, in the original consent form or medical record) that a copy of the consent form and subject information form have been provided to the subject.

[Items to be explained to the subjects]

1. That the study involves research
2. Study objectives
3. Study methods (including experimental aspect of the study, inclusion criteria for subjects and, if subjects are randomized to treatment arms, the probability of randomization to each treatment)
4. Planned duration of participation in the study
5. Planned number of subjects in the study
6. Foreseeable physical and mental benefits (or if no such benefit, a statement to that effect) and risks associated with the study drug
7. Whether or not there are other treatment methods, and if any, expected important benefits and risks of the methods
8. Compensation and treatment that the subject can receive if any study-related injury occurs as a result of participation in the study
9. Statements that participation in the study is based on the subject's own free will; that the subject can refuse to participate in, or withdraw from, the study at any time; that he/she will not be disadvantaged even if he/she refuses to participate in or withdraw from the study; and that he/she will not lose any benefits that would have been given, even if he/she does not participate in the study
10. A statement that the subject will be promptly informed if any information that may affect his/her willingness to continue participation in the study is obtained
11. Conditions or reasons for withdrawal from the study
12. Statements that the Clinical Research Associates, responsible auditors, IRB, and regulatory authorities can access source documents; that in such a case, the

subject's privacy will be protected; and that the subject is deemed to have consented to such access by writing his/her name and affixing his/her seal on or signing the consent form

13. A statement that the subject's privacy will be protected even if the results of the study are published
14. Details of expenses the subject needs to pay, if any
15. Details of payment to the subject, if any
16. Name, title, and contact information of the investigator or subinvestigator
17. Contact information of the study center in the event that the subject requires further information regarding the study or the rights of subjects, or in the event of study-related injury
18. Responsibilities of subjects
19. The type of IRB that evaluates and reviews the appropriateness of the study, etc., items to be evaluated and reviewed by the IRB, and other matters regarding the IRB in relation to the study

15.4. Informed Consent for Biomarker Study

The investigator or subinvestigator will explain the details of the study listed below to subjects in a readily understandable way to confirm their willingness to provide consent to participate in the biomarker research on their free will, and obtain the result in writing. The investigator or subinvestigator will ensure that the subject's decision on the consent has been entered in the concerned section of the informed consent form.

1. Characteristics and properties of genetic information
2. Study objectives
3. Study methods
4. Foreseeable physical and mental benefits and risks associated with the study
5. Statements that participation in the biomarker study is based on the subject's own free will and that the subject can refuse to participate in, or withdraw from, the study at any time; that he/she will not be disadvantaged even if he/she withdraws his/her consent
6. Handling of specimens and data after withdrawal of consent
7. Matters on the method of handling, duration of storage, and disposal of specimens
8. Compensation that the subject can receive
9. Disclosure of study results and to whom the results belong
10. Details of expenses the subject needs to pay, if any
11. A statement that no payment is made for specimens provided by the subject
12. Protection of human rights, including the subject's privacy

15.5. Informed Consent for Storage (Banking) of Specimens for Genome/Gene Analysis

The investigator or subinvestigator will explain the items relating to banking listed below, in addition to the information given in "Section 15.3 Procedures for Informed Consent" and "Section 15.4 Informed Consent for Biomarker Study," to subjects who have provided informed consent for this clinical study in a readily understandable way using the informed consent form for storage (banking) of specimens for genome/gene analysis, and will obtain written informed consent for banking on their free will, separately from consent to participate in the clinical study.

1. Characteristics and properties of genetic information
2. Policy for specimen and data handling in the case of consent withdrawal
3. Policy for specimen handling after the completion of genotyping
4. Procedures for handling banked specimens and banking period
5. Disclosure of genotyping results

Even if subjects refuse to participate in or have withdrawn from banking, they may continue participating in the clinical study unless their willingness to participate in any part of the study except for banking is changed. Subjects may refuse to participate or withdraw from banking without penalty or loss of benefits to which they are otherwise entitled.

15.6. Provision of New Information Affecting the Conduct of the Study

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

15.7. Planned Study Period

06 Jul 2018 to 31 Dec 2019

15.8. Protocol Amendment

If any amendment has to be made to the clinical study protocol after the start of the study, the sponsor will examine the appropriateness of the amendment and potential influences on the evaluations in the study, and after discussion with the medical expert, etc., if necessary, determine whether to make the amendment or not. The sponsor will clearly document and retain the content of the discussion, whether to amend the protocol or not and the reason, etc.

The sponsor will promptly notify the investigator of the specific details of the amendment to the protocol. If the protocol is updated to a new version, the sponsor will newly obtain written agreement of the investigator and implement the procedures specified by the study center.

15.9. Permanent or Temporary Discontinuation of the Study

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

1. If any new safety information regarding the study drug, or information regarding SAEs is obtained
2. If any major GCP violation or significant protocol deviation is committed by the sponsor, the study center, or the investigator
3. If any other new information of such relevance is obtained during the study

If the sponsor decides to discontinue the study entirely after consultation with the medical expert, etc., the sponsor will promptly notify the head of the study center in writing with the reason for the discontinuation. The head of the study center will promptly notify the investigator and the IRB in writing of the discontinuation and the reason for discontinuation.

If the study is discontinued permanently or temporarily for any reason, the investigator will promptly notify the subjects participating in the study of the fact, and take appropriate actions and perform the necessary tests to verify the safety of subjects.

15.10. Procedures for Preparing the Case Report Form and Remarks

In this study, case report forms will be prepared by the investigator, and measurement reports of 12-lead ECGs, pharmacokinetics, and biomarkers will be prepared at each measurement facility. The preparation method of each measurement result report, etc. will be separately specified.

15.10.1. Style of the Case Report Form

In this study, an electronic case report form will be recorded using the electronic data capturing (EDC) system (Table 15.10.1 EDC System), which is designed to prepare electronic case report forms. The case report form (including an audit trail) will be

prepared for each subject and the one that was signed by the investigator will be handled as the original. A validated EDC system will be used in the study.

Table 15.10.1: EDC System

EDC system name	Medidata Rave®
EDC system development corporation	Medidata Solutions, Inc.
How to enter data	Data entry via the web interface
Terminal for data entry	PC at the study center
OS prohibited	None
Browser	Medidata Rave supports any browser that conforms to HTML 4, HTML 5, and CSS2. JavaScript needs to be enabled in the browser.
Recommended screen resolution	1024 × 764 resolution or higher
Recommended connection speed	128 kbps or higher
Others	Adobe Flash Player: Version 10 or higher

15.10.2. Completion of the Case Report Forms

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

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

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

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

15.10.4. Changes or Corrections to the Case Report Form

1. Any corrections to the case report form will be made by the investigator, subinvestigator, or study staff in accordance with the "Guidance for Completing and Making Corrections to the Case Report Form" provided by the sponsor.
2. The investigator is responsible for the descriptions in the case report form, and will retain copies of all records, including changes or corrections.

15.11. Retention of Source Documents and Other Records

15.11.1. Definition of Source Documents

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

15.11.2. Record Keeping

15.11.2.1. Institutional Review Board

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

1. Date of approval of DS-3032b (or if clinical development is discontinued, 3 years after the date of notification of the discontinuation by the sponsor)
2. Three years after discontinuation or completion of the study

15.11.2.2. Study Center

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

The head of the study center or the person responsible for record keeping will take measures to prevent loss or disposal of these records during the relevant period and provide immediate access to them upon request.

1. Date of approval of the DS-3032b (or if clinical development is discontinued, 3 years after the date of notification of the discontinuation from the sponsor)

2. Three years after discontinuation or completion of the study

To respond to subject's withdrawal of consent for long-term storage (banking) of specimens for genome/gene analysis, which may arise after the end of the study, the study center will retain the subject screening list for up to 20 years after the end of the study.

15.11.2.3. Sponsor

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

1. Five years after the date of approval of the DS-3032b (or if clinical development is discontinued, 3 years after the date of the decision on discontinuation) or the date of completion of the reexamination, whichever is later
2. Three years after discontinuation or completion of the study

15.12. Source Document Verification

The head of the study center and the investigator will provide direct access to all study-related documents, including source documents, at the implementation of monitoring and auditing by the sponsor as well as inspections by the regulatory authorities and the IRB. The sponsor will have direct access to all study-related documents, including source documents, at the study center when performing monitoring and auditing to ensure appropriate implementation of the study and the reliability of the data. The sponsor will confer with the investigator in advance regarding the procedures for source document verification.

15.13. Organization

The study organization is given in Attachment 1.

16. REFERENCES

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17. APPENDICES

Appendix 1 Schedule of Study Procedures

Appendix 2 Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)

Appendix 3 New York Heart Association (NYHA) Functional Classification

Appendix 1

Schedule of Study Procedures and Specimen Collection (Subtrial A: 14/28 Day Schedule)

Cycle[a]	Screening	Cycle 1														Cycle 2				Cycle 3	Cycle 4 and thereafter	Assessment at withdrawal[b]	Follow-up[c]
Study treatment		**Subjects will take the study drug once daily on Days 1 to 14 of each cycle. (Meal consumption should be avoided from 2 hours pre-dose to 1 hour post-dose.)**																					
Cycle Day		1						2	8	14						22	1		14	1	1		
Acceptable time window (day)	−14								±2							±2			−4	−4	−4	±3	±5
Elapsed time from administration (hours)		Pre-dose	1	2	3	6	8	Pre-dose	Pre-dose	Pre-dose	1	2	3	6	8		Pre-dose	3	Pre-dose	Pre-dose	Pre-dose		
Informed consent[d]	●																						
Baseline subject characteristics	●																						
Confirmation of medical history/ complications	●																						
Confirmation of inclusion/exclusion criteria[e]	●																						
Viral marker test[f]	●																						
Pregnancy test[g]	●																			●			
Assessment of AEs[h]	⟷																						
Confirmation of concomitant drugs/ therapies	⟷																						
ECOG PS assessment, body weight measurement	●	●[i]							●	●						●	●		●	●	●	●	●
Height measurement	●																						
Vital signs measurement[j]	●	●[i]			●			●	●	●			●			●	●		●	●	●	●	●
Laboratory tests (Hematology test, blood biochemistry test, coagulation test, urine collection)	●	●[i]						●	●	●						●	●		●	●	●	●	●
12-lead ECG measurement[k] (including evaluation of QTcF)	●	●			●			●	●	●			●			●	●		●	●	●	●	●
Bone marrow and peripheral blood assessment	●																●[l]			●[l]	●[l]	●[l]	○[m]
Biomarkers: Serum		●						●	●[n]	●						●[n]	●						
Biomarkers: Blood and bone marrow	●																					●	○[m]
Collection of specimens for PGx[o]	●																						
Blood collection for pharmacokinetics		●	●	●	●	●	●	●	●[p]	●	●	●	●	●	●		●	●					

[a] Each cycle is 28 days long, and DLT evaluation will be conducted at the end of Cycle 1.
[b] Examinations and assessments will be performed on the day (±3 days) when the investigator or subinvestigator decides subject's withdrawal from the study. When the subject withdraws from the study on Day 25 or later based on the day of the last dose of the study drug defined as Day 0, examinations and assessments will be omitted and Follow-up will be performed immediately.
[c] Examinations and assessments will be performed on Day 30 (±5 days) based on the day of the last dose of the study drug defined as Day 0. If a subsequent AML treatment is introduced, Follow-up will be performed before the start of the subsequent AML treatment.
[d] Will be obtained before screening tests.
[e] If the study treatment is started on Day 8 or later based on the day of registration defined as Day 0, the subject's eligibility should be assessed again on the preceding day or the start day (before administration) of study treatment.
[f] Will be confirmed within 90 days before the day of registration.
[g] Will be performed only for female subjects of childbearing potential (using urine or serum specimens).
[h] SAEs will be collected (non-SAEs will not be collected) during the period from informed consent obtainment to before the first dose of the study drug.
[i] Examinations and assessments on Day 1 of Cycle 1 are not necessary when they are performed within 24 hours before the first dose of the study drug.
[j] Axillary body temperature, pulse rate, and systolic and diastolic blood pressure will be measured at rest.
[k] A 12-lead ECG will be performed in the supine position after a 10-minute rest. Each measurement will be performed in triplicate at approximately 1- to 5-minute intervals.
[l] The acceptable time window for bone marrow and peripheral blood assessment on Day 1 of Cycle 2 and thereafter is Day 25 of the previous cycle to pre-dose on Day 1 of the present cycle. After CR is achieved, assessment based on bone marrow findings may be skipped until blasts are observed in the peripheral blood.
[m] Will be performed when the assessment at withdrawal is omitted.
[n] The acceptable time window for blood collection for biomarkers on Day 8 of Cycle 1 and Day 22 of Cycle 1 is ±0 days.
[o] Will be performed only for subjects who have provided informed consent for the PGx study.
[p] The acceptable time window for blood collection for pharmacokinetics on Day 8 of Cycle 1 is ±0 days.

Schedule of Study Procedures and Specimen Collection (Subtrial B: 7/28 Day Schedule)

Cycle[a]	Screening	Cycle 1															Cycle 2				Cycle 3	Cycle 4 and thereafter	Assessment at withdrawal[b]	Follow-up[c]
Study treatment		**Subjects will take the study drug once daily on Days 1 to 7 of each cycle. (Meal consumption should be avoided from 2 hours pre-dose to 1 hour post-dose.)**																						
Cycle Day		**1**						**2**	**7**						**8**	**15**	**22**	**1**		**7**	**22**	**1**	**1**		
Acceptable time window (day)	**−14**															**±2**	**±2**			**−2**	**±2**	**−4**	**−4**	**±3**	**±5**
Elapsed time from administration (hours)		**Pre-dose**	**1**	**2**	**3**	**6**	**8**	**Pre-dose**	**Pre-dose**	**1**	**2**	**3**	**6**	**8**				**Pre-dose**	**3**	**Pre-dose**		**Pre-dose**	**Pre-dose**		
Informed consent[d]	●																								
Baseline subject characteristics	●																								
Confirmation of medical history/ complications	●																								
Confirmation of inclusion/ exclusion criteria[e]	●																								
Viral marker test[f]	●																								
Pregnancy test[g]	●																					●			
Assessment of AEs[h]	←																								→
Confirmation of concomitant drugs/ therapies	←																								→
ECOG PS assessment, body weight measurement	●	●[i]							●							●	●	●		●	●	●	●	●	●
Height measurement	●																								
Vital signs measurement[j]	●	●[i]			●			●	●			●				●	●	●		●	●	●	●	●	●
Laboratory tests (Hematology test, blood biochemistry test, coagulation test, urine collection)	●	●[i]						●	●							●	●	●		●	●	●	●	●	●
12-lead ECG measurement[k] (including evaluation of QTcF)	●	●			●			●	●			●				●	●	●		●	●	●	●	●	●
Bone marrow and peripheral blood assessment	●																	●[l]				●[l]	●[l]	●[l]	○[m]
Biomarkers: Serum		●						●	●									●							
Biomarkers: Blood and bone marrow	●																							●	○[m]
Collection of specimens for PGx[n]	●																								
Blood collection for pharmacokinetics		●	●	●	●	●	●	●	●	●	●	●	●	●	●[o]			●	●						

[a] Each cycle is 28 days long, and DLT evaluation will be conducted at the end of Cycle 1.
[b] Examinations and assessments will be performed on the day (±3 days) when the investigator or subinvestigator decides subject's withdrawal from the study.
When the subject withdraws from the study on Day 25 or later based on the day of the last dose of the study drug defined as Day 0, examinations and assessments will be omitted and Follow-up will be performed immediately.
[c] Examinations and assessments will be performed on Day 30 (±5 days) based on the day of the last dose of the study drug defined as Day 0. If a subsequent AML treatment is introduced, Follow-up will be performed before the start of the subsequent AML treatment.
[d] Will be obtained before screening tests.
[e] If the study treatment is started on Day 8 or later based on the day of registration defined as Day 0, the subject's eligibility should be assessed again on the preceding day or the start day (before administration) of study treatment.
[f] Will be confirmed within 90 days before the day of registration.
[g] Will be performed only for female subjects of childbearing potential (using urine or serum specimens).
[h] SAEs will be collected (non-SAEs will not be collected) during the period from informed consent obtainment to before the first dose of the study drug.
[i] Examinations and assessments on Day 1 of Cycle 1 are not necessary when they are performed within 24 hours before the first dose of the study drug.
[j] Axillary body temperature, pulse rate, and systolic and diastolic blood pressure will be measured at rest.
[k] A 12-lead ECG will be performed in the supine position after a 10-minute rest. Each measurement will be performed in triplicate at approximately 1- to 5-minute intervals.
[l] The acceptable time window for bone marrow and peripheral blood assessment on Day 1 of Cycle 2 and thereafter is Day 25 of the previous cycle to pre-dose on Day 1 of the present cycle. After CR is achieved, assessment based on bone marrow findings may be skipped until blasts are observed in the peripheral blood.
[m] Will be performed when the assessment at withdrawal is omitted.
[n] Will be performed only for subjects who have provided informed consent for the PGx study.
[o] Will be performed at 24 h post-dose of Day 7.

Schedule of Study Procedures and Specimen Collection (Subtrial C: 3/14 Day × 2 Schedule)

Cycle[a]		Screening	Cycle 1																			Cycle 2				Cycle 3	Cycle 4 and thereafter	Assessment at withdrawal[b]	Follow-up[c]
Study treatment			**Subjects will take the study drug once daily on Days 1 to 3 and Days 15 to 17 of each cycle. (Meal consumption should be avoided from 2 hours pre-dose to 1 hour post-dose.)**																										
Cycle Day			1						2	3					4	8	15		16	17		22	1		3	15 17	1	1		
Acceptable time window (day)		−14														±2						±2					−4	−4	±3	±5
Elapsed time from administration (hours)			Pre-dose	1	2	3	6	8	Pre-dose	Pre-dose	1	2	3	6	8			Pre-dose	3	Pre-dose	Pre-dose	3		Pre-dose	3	Pre-dose	Pre-dose	Pre-dose	Pre-dose		
Informed consent[d]		●																												
Baseline subject characteristics		●																												
Confirmation of medical history/ complications		●																												
Confirmation of inclusion/ exclusion criteria[e]		●																												
Viral marker test[f]		●																												
Pregnancy test[g]		●																									●			
Assessment of AEs[h]		←																												→
Confirmation of concomitant drugs/therapies		←																												→
ECOG PS assessment, body weight measurement		●	●[i]							●						●	●			●		●	●		●	●	●	●	●	●
Height measurement		●																												
Vital signs measurement[j]		●	●[i]			●				●			●				●	●	●		●	●	●		●		●	●	●	●	●
Laboratory tests (Hematology test, blood biochemistry test, coagulation test, urine collection)		●	●[i]							●							●	●			●		●		●	●	●	●	●	●
12-lead ECG measurement[k] (including evaluation of QTcF)		●	●			●				●			●				●	●	●		●	●	●		●	●	●	●	●	●
Bone marrow and peripheral blood assessment		●																					●[l]				●[l]	●[l]	●[l]	○[m]
Biomarkers	Serum		●						●	●							●		●	●			●							
	Blood and bone marrow	●																											●	○[m]
Collection of specimens for PGx[n]		●																												
Blood collection for pharmacokinetics			●	●	●	●	●	●	●	●	●	●	●	●	●	●[o]		●		●	●			●	●					

[a] Each cycle is 28 days long, and DLT evaluation will be conducted at the end of Cycle 1.
[b] Examinations and assessments will be performed on the day (±3 days) when the investigator or subinvestigator decides subject's withdrawal from the study.
When the subject withdraws from the study on Day 25 or later based on the day of the last dose of the study drug defined as Day 0, examinations and assessments will be omitted and Follow-up will be performed immediately.
[c] Examinations and assessments will be performed on Day 30 (±5 days) based on the day of the last dose of the study drug defined as Day 0. If a subsequent AML treatment is introduced, Follow-up will be performed before the start of the subsequent AML treatment.
[d] Will be obtained before screening tests.
[e] If the study treatment is started on Day 8 or later based on the day of registration defined as Day 0, the subject's eligibility should be assessed again on the preceding day or the start day (before administration) of study treatment.
[f] Will be confirmed within 90 days before the day of registration.
[g] Will be performed only for female subjects of childbearing potential (using urine or serum specimens).
[h] SAEs will be collected (non-SAEs will not be collected) during the period from informed consent obtainment to before the first dose of the study drug.
[i] Examinations and assessments on Day 1 of Cycle 1 are not necessary when they are performed within 24 hours before the first dose of the study drug.
[j] Axillary body temperature, pulse rate, and systolic and diastolic blood pressure will be measured at rest.
[k] A 12-lead ECG will be performed in the supine position after a 10-minute rest. Each measurement will be performed in triplicate at approximately 1- to 5-minute intervals.
[l] The acceptable time window for bone marrow and peripheral blood assessment on Day 1 of Cycle 2 and thereafter is Day 25 of the previous cycle to pre-dose on Day 1 of the present cycle. After CR is achieved, assessment based on bone marrow findings may be skipped until blasts are observed in the peripheral blood.
[m] Will be performed when the assessment at withdrawal is omitted.
[n] Will be performed only for subjects who have provided informed consent for the PGx study.
[o] Will be performed at 24 h post-dose of Day 3.

Schedule of Study Procedures and Specimen Collection (Subtrial D: 21/28 Day Schedule)

Cycle[a]	Screening	Cycle 1														Cycle 2					Cycle 3	Cycle 4 and thereafter	Assessment at withdrawal[b]	Follow-up[c]
Study treatment		**Subjects will take the study drug once daily on Days 1 to 21 of each cycle. (Meal consumption should be avoided from 2 hours pre-dose to 1 hour post-dose.)**																						
Cycle Day		1						2	8	15						21		1		15	21	1	1		
Acceptable time window (day)	−14								±2											±2	−2	−4	−4	±3	±5
Elapsed time from administration (hours)		Pre-dose	1	2	3	6	8	Pre-dose	Pre-dose	Pre-dose	1	2	3	6	8	Pre-dose	3	Pre-dose	3	Pre-dose	Pre-dose	Pre-dose	Pre-dose		
Informed consent[d]	●																								
Baseline subject characteristics	●																								
Confirmation of medical history/ complications	●																								
Confirmation of inclusion/ exclusion criteria[e]	●																								
Viral marker test[f]	●																								
Pregnancy test[g]	●																					●			
Assessment of AEs[h]	←																								→
Confirmation of concomitant drugs/ therapies	←																								→
ECOG PS assessment, body weight measurement	●	●[i]							●	●						●		●		●	●	●	●	●	●
Height measurement	●																								
Vital signs measurement[j]	●	●[i]			●			●	●	●						●	●	●		●	●	●	●	●	●
Laboratory tests (Hematology test, blood biochemistry test, coagulation test, urine collection)	●	●[i]						●	●	●						●		●		●	●	●	●	●	●
12-lead ECG measurement[k] (including evaluation of QTcF)	●	●			●			●	●	●						●	●	●		●	●	●	●	●	●
Bone marrow and peripheral blood assessment	●																	●[l]				●[l]	●[l]	●[l]	○[m]
Biomarkers: Serum		●						●		●						●		●							
Biomarkers: Blood and bone marrow	●																							●	○[m]
Collection of specimens for PGx[n]	●																								
Blood collection for pharmacokinetics		●	●	●	●	●	●	●	●[o]	●	●	●	●	●	●	●		●	●						

[a] Each cycle is 28 days long, and DLT evaluation will be conducted at the end of Cycle 1.
[b] Examinations and assessments will be performed on the day (±3 days) when the investigator or subinvestigator decides subject's withdrawal from the study. When the subject withdraws from the study on Day 25 or later based on the day of the last dose of the study drug defined as Day 0, examinations and assessments will be omitted and Follow-up will be performed immediately.
[c] Examinations and assessments will be performed on Day 30 (±5 days) based on the day of the last dose of the study drug defined as Day 0. If a subsequent AML treatment is introduced, Follow-up will be performed before the start of the subsequent AML treatment.
[d] Will be obtained before screening tests.
[e] If the study treatment is started on Day 8 or later based on the day of registration defined as Day 0, the subject's eligibility should be assessed again on the preceding day or the start day (before administration) of study treatment.
[f] Will be confirmed within 90 days before the day of registration.
[g] Will be performed only for female subjects of childbearing potential (using urine or serum specimens).
[h] SAEs will be collected (non-SAEs will not be collected) during the period from informed consent obtainment to before the first dose of the study drug.
[i] Examinations and assessments on Day 1 of Cycle 1 are not necessary when they are performed within 24 hours before the first dose of the study drug.
[j] Axillary body temperature, pulse rate, and systolic and diastolic blood pressure will be measured at rest.
[k] A 12-lead ECG will be performed in the supine position after a 10-minute rest. Each measurement will be performed in triplicate at approximately 1- to 5-minute intervals.
[l] The acceptable time window for bone marrow and peripheral blood assessment on Day 1 of Cycle 2 and thereafter is Day 25 of the previous cycle to pre-dose on Day 1 of the present cycle. After CR is achieved, assessment based on bone marrow findings may be skipped until blasts are observed in the peripheral blood.
[m] Will be performed when the assessment at withdrawal is omitted.
[n] Will be performed only for subjects who have provided informed consent for the PGx study.
[o] The acceptable time window for blood collection for pharmacokinetics on Day 8 of Cycle 1 is ±0 days.

Appendix 2

Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)

Score	ECOG PS
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

EOCG

Appendix 3

New York Heart Association (NYHA) Functional Classification

Class	Symptoms
Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.