CLINICAL STUDY PROTOCOL

Phase 1 Study of SGI-110 in Patients With Acute Myeloid Leukemia
(Phase 1 Trial)

NCT Number: NCT02293993
PRT NO.: 343-14-001
Version Date: 13 October 2017 (Version 8)

Phase 1 Study of SGI-110 in Patients With Acute Myeloid Leukemia

(Phase 1 Trial)

Clinical Protocol

Protocol No.: 343-14-001

(Translated Version)

Confidential

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Version 8: 13 Oct 2017

Statement of Confidentiality

The trial protocol is to be treated as confidential information and is to be made available only to persons involved in the trial. The content of the protocol is not to be disclosed to any third party without the prior written consent of Otsuka Pharmaceutical Co., Ltd., except in the case of its being explained to a candidate trial subject. Disclosure of the results of the trial to academic societies or journals, etc, in part or in whole, will require the prior written approval of Otsuka Pharmaceutical Co., Ltd.

Trial Protocol Synopsis

<table>
<tr><td>Name of Test Product</td><td>SGI-110</td></tr>
<tr><td>Trial Title</td><td>Phase 1 study of SGI-110 in patients with acute myeloid leukemia.</td></tr>
<tr><td>Trial Objectives</td><td>Primary:
• To evaluate the tolerability of SGI-110 when administered subcutaneously to Japanese patients with acute myeloid leukemia (AML)
Secondary:
• To perform pharmacokinetic (PK) evaluation of plasma SGI-110 and decitabine
• To evaluate efficacy (complete remission rate, composite complete remission rate, overall remission rate, overall survival, composite complete remission duration)
• To evaluate safety through observed adverse events (AEs) and examinations
Exploratory:
• To perform pharmacodynamic (PD) evaluation of the extent of DNA hypomethylation</td></tr>
<tr><td>Phase of Development</td><td>Phase: 1
Type of trial: Exploratory trial, dose-finding trial, PK trial.</td></tr>
<tr><td>Method</td><td>After being reconstituted using the custom diluent provided with the investigational medicinal product (IMP), SGI-110 will be administered subcutaneously at a daily dose determined through calculation of each subject's body surface area (BSA) prior to administration of the IMP in each course, according to each cohort.
Each course will consist of 4 weeks (28 days). In Cohorts 1, 2, and 4, subjects will receive SGI-110 once daily for 5 consecutive days (Day 1 to Day 5), followed by a 23-day non-dosing period (Day 6 to Day 28). In Cohort 3, subjects will receive SGI-110 once daily for 10 days in total (SGI-110 will be administered for 5 consecutive days [Day 1 to Day 5], suspended for 2 days [Day 6 and Day 7], then administered for another 5 consecutive days [Day 8 to Day 12]), followed by a 16-day non-dosing period (Day 13 to Day 28).
The sponsor will confirm the incidence of dose-limiting toxicity (DLT) during the DLT evaluation period in each cohort and judge the transition to the next cohort based on the advice of the Independent Data Monitoring Committee.
If the number of subjects exhibiting DLT within a cohort is ≥ 2/3 or ≥ 2/6, then there will be no transition to the next cohort, and the maximum tolerated dose (MTD) will be determined as follows:
<table>
<tr><td>≥ 2/3 or ≥ 2/6 subjects with DLT</td><td>MTD</td></tr>
<tr><td>In Cohort 1</td><td>< 36 mg/m^2 in 5-day regimen</td></tr>
<tr><td>In Cohort 2</td><td>36 mg/m^2 in 5-day regimen</td></tr>
<tr><td>In Cohort 4</td><td>60 mg/m^2 in 5-day regimen</td></tr>
</table>
If the incidence of DLT does not reach either ≥ 2/3 or ≥ 2/6 in any of the cohorts in the table above, the MTD will not be determined in this study. For Cohort 3, DLT will be evaluated but the MTD for 10-day regimen will not be determined from the incidence of DLT.

[Definition of dose-limiting toxicity]
Dose-limiting toxicity shall be defined as any of the following AEs occurring during Course 1 for which there is a reasonable probability or possibility of a causal relationship with the IMP if it cannot be reasonably explained by underlying disease, intercurrent illness, or concomitant medications. The severity of AEs will be graded in accordance with Common Terminology Criteria for</td></tr>
</table>

	Adverse Events (CTCAE) version 4.0. • Non-hematologic toxicity of Grade 3 or higher, except for the following: – Nausea, vomiting, or diarrhea of Grade 3 that is controllable by optimal therapy – Grade 3 laboratory findings other than serum creatinine (Cr), bilirubin, aspartate aminotransferase (AST), or alanine aminotransferase (ALT), that are not associated with clinical manifestations • Grade 4 thrombocytopenia that was not present at study entry and that is not resolved within 7 days • Grade 4 neutropenia that was not present at study entry and that is not resolved within 7 days • Febrile neutropenia [Note] If the febrile neutropenia is not resolved or improved during the DLT evaluation period, it shall be defined as DLT. If the febrile neutropenia is resolved or improved during the DLT evaluation period, it shall be judged whether it is defined as DLT based on the background of the subject and through consultation with the Independent Data Monitoring Committee. • Any AE that results in a delay of > 4 weeks in starting the next treatment course [Note] In this trial, febrile neutropenia is defined as a neutrophil count of < 500/μL accompanied by a fever of ≥ 38°C. The DLT evaluation period will be for the duration of Course 1. Subjects who complete IMP administration and all observations during the DLT evaluation period, and who do not have any apparent progression of AML, will be permitted to continue treatment with IMP following the DLT evaluation period if they wish. The primary evaluation data for Cohorts 1, 2, and 4 will have a cutoff date of 31 May 2016 and the data for Cohort 3 will have a cutoff date of 30 Nov 2017. The period up until the data cutoff will be defined as the primary evaluation part. This will be followed by an extended treatment part to assess long-term safety, which will include those subjects on IMP treatment who have consented to participate in the extended treatment part. Transition from the primary evaluation part to the extended treatment part will take place at the start of the next course after the data cutoff.
Target Disease or Symptom	AML
Number of Patients	Maximum: 24 subjects Cohort 1 (36 mg/m^2, 5 days): 3 to 6 subjects Cohort 2 (60 mg/m^2, 5 days): 3 to 6 subjects Cohort 3 (60 mg/m^2, 10 days [ie, 5-day administration twice, with a non-dosing period in-between]): 6 subjects Cohort 4 (90 mg/m^2, 5 days): 3 to 6 subjects
Inclusion Criteria	Patients meeting all of the following criteria at the time of screening will be included in this trial: 1) Male or female patients with a diagnosis of AML (World Health Organization [WHO] classification 2008). • Patients, 20 years of age or older, who are unresponsive to standard chemotherapy or have relapsed following standard chemotherapy • Patients, 65 years of age or older, who are not eligible for standard intensive chemotherapy and who meet at least one of the following

	criteria (applicable to Cohorts 1, 2, and 4 only): – AML from myelodysplastic syndrome (MDS), or secondary AML – Chromosomal karyotype abnormality with poor prognosis [del (5q), del (7q), −5, −7, abnormality of 3q (q21;q26), t (6;9) (p23;q34), t (9;22) (q34;q11.2), abnormality of 11 (11q23), or complex karyotype of 3 or more unrelated abnormalities of any kind] – Dysfunction of the heart (left ventricular ejection fraction [LVEF] < 50%) or lung (diffusing capacity of the lung for carbon monoxide [DLCO] or forced expiratory volume in the first second [FEV 1] < 50% of expected value) which is unrelated to AML – Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 – 75 years of age or older 2) Patients with ECOG PS of 0 to 2. 3) Patients with adequate vital organ function (patients whose clinical laboratory values meet the following conditions). a) Hepatic function: total bilirubin (T-Bil) ≤ 2 × upper limit of normal (ULN); AST and ALT ≤ 2.5 × ULN. b) Renal function: serum Cr ≤ 1.5 × ULN. 4) Female patients of childbearing potential must not be pregnant or breast feeding (pregnancy test will be performed at screening). Female patients of childbearing potential and all male patients must practice two medically acceptable methods of birth control and must not become pregnant or father a child while receiving treatment with SGI-110 and for 3 months following last dosing. 5) Patients who have undergone prior allogeneic hematopoietic stem cell transplantation must have no evidence of active graft-versus host disease (GVHD) and must be off immunosuppressive therapy by ≥ 2 weeks prior to the scheduled start of IMP administration. 6) Patients who have undergone no major surgery within 4 weeks prior to the scheduled start of IMP administration. 7) Patients who have undergone no chemotherapy within 2 weeks prior to the scheduled start of IMP administration, nor hematopoietic stem cell transplantation within 8 weeks prior to the scheduled start of IMP administration. 8) Patients who are able to provide written consent to participate in this trial by signing an informed consent form (ICF) that has been approved by an Institutional Review Board (IRB) (patients who are willing to comply with the protocol, including consent to hospitalization during Course 1).
Exclusion Criteria	Patients falling under any of the following criteria at the time of screening will be excluded from this trial: 1) Patients with acute promyelocytic leukemia (APL) accompanied by t (15;17) (q22;q12) or (PML/RARA) karyotype abnormalities (including other variant types of APL). 2) Patients with multiple cancers (except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for at least 3 years).

	3) Patients with life-threatening illnesses other than AML, such as uncontrolled medical conditions or organ system dysfunction which, in the opinion of the investigator or subinvestigator, could compromise the subject's safety or the study outcomes. 4) Patients with poorly controlled arrhythmias, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association (NYHA) Functional Classification. 5) Patients with symptomatic central nervous system involvement. 6) Patients who have received radiation therapy for extramedullary disease within 2 weeks prior to planned enrollment. 7) Patients with AEs (other than alopecia) of Grade 2 or higher from prior therapy for AML, at the time of screening for this trial. 8) Patients with febrile neutropenia. 9) Patients who are human immunodeficiency virus (HIV) antibody positive, hepatitis B virus (HBV)-DNA positive, or with active hepatitis C. 10) Patients who have taken any investigational drug or individually imported drug within 2 weeks prior to the scheduled start of IMP administration. 11) Patients who have been treated with systemic corticosteroids as treatment for their AML within 2 weeks prior to the scheduled start of IMP administration. 12) Patients with uncontrolled active systemic infections. 13) Patients who have hypersensitivity to decitabine, SGI-110, or IMP excipients. 14) Patients judged to be ineligible by the investigator or subinvestigator for any other reason.
Discontinuation Criteria	1) Apparent progression (including the relapse) of the primary disease. 2) DLT that does not improve to the baseline level or show improvement by at least 1 grade within 4 weeks, or occurrence of another DLT. 3) Delay in commencement of the next course by more than 4 weeks due to an AE, unless the investigator or subinvestigator judges that continuation of SGI-110 administration is in the patient's best interest, in which case the delay may be extended by another 2 weeks. 4) Subject becomes pregnant. 5) Subject wishes to withdraw from the trial. 6) The investigator or subinvestigator judges that it is difficult to continue IMP administration due to occurrence of an AE. 7) The investigator or subinvestigator judges that it is necessary to discontinue IMP administration for any other reason.
Investigational Medicinal Products, Dose and Regimen, and Treatment Period	[Investigational medicinal product] SGI-110 for injection, 100 mg: A 5-mL glass vial contains SGI-110 equivalent to 100 mg of free acid, as a lyophilized powder. SGI-110 diluent for reconstitution, 3 mL: A 5-mL glass vial contains 3 mL of custom diluent for reconstitution. [Dose and regimen, treatment period] The total daily dose will be determined based on the subject's BSA calculated from height and weight prior to administration in each course, according to the treatment cohort. SGI-110 will be administered subcutaneously at the determined daily dose after being reconstituted using the custom diluent provided.

	In Cohorts 1, 2, and 4, subjects will receive SGI-110 once daily for 5 consecutive days (Day 1 to Day 5), followed by a 23-day non-dosing period (Day 6 to Day 28). One course will consist of 4 weeks (28 days). In Cohort 3, subjects will receive SGI-110 once daily for 10 days in total (SGI-110 will be administered for 5 consecutive days [Day 1 to Day 5], suspended for 2 days [Day 6 and Day 7], then administered for another 5 consecutive days [Day 8 to Day 12]), followed by a 16-day non-dosing period (Day 13 to Day 28). One course will consist of 4 weeks (28 days). Refer to Section 6 Trial Design, for the detailed dose and regimen after the DLT evaluation period. The dose and regimen for each cohort is as follows: Cohort 1 (36 mg/m^2, 5-day administration) Cohort 2 (60 mg/m^2, 5-day administration) Cohort 3 (60 mg/m^2, 10-day administration [ie, 5-day administration twice, with a non-dosing period in-between]) Cohort 4 (90 mg/m^2, 5-day administration)
Prohibited Concomitant Drugs or Therapies	Only the IMP will be used for treating the primary disease, and concomitant use of the drugs and therapies listed below is prohibited from the time of informed consent to the end of the withdrawal examination. • Other anti-cancer drugs, hormone therapy, antibody therapy, radiation therapy, thermal therapy, or other anti-cancer therapies • Other investigational drugs and individually imported drugs • Prophylactic therapies for the purpose of preventing AEs (except infection) (Prophylactic therapies to prevent recurrence of AEs observed after the start of the IMP administration will be allowed.)
Endpoints	Safety <Primary endpoint> • DLT <Secondary endpoints> • AEs, clinical laboratory values, vital signs (blood pressure, pulse rate, body temperature), body weight, ECOG PS, 12-lead electrocardiogram (ECG), chest X-ray Efficacy endpoints • Complete remission rate, composite complete remission rate, overall remission rate, overall survival, and composite complete remission duration Pharmacokinetic endpoints • SGI-110 and decitabine plasma concentrations, PK parameters Pharmacodynamics endpoint • Extent of DNA hypomethylation in long interspersed nucleotide element-1 (LINE-1)
Scheduled Trial Duration	Overall trial duration: 01 Oct 2014 to 31 Dec 2019 1) Cohorts 1, 2, and 4 (Primary evaluation part [Cohorts 1, 2, and 4]) 01 Oct 2014 to 31 May 2016 (Extended treatment part [Cohorts 1, 2, and 4]) 01 Jun 2016 to 31 Dec 2019 2) Cohort 3 (Primary evaluation part [Cohort 3]) 01 Sep 2016 to 30 Nov 2017 (Extended treatment part [Cohort 3]) 01 Dec 2017 to 31 Dec 2019

Schedule of Events (Refer to 7.1 Schedule and Procedures) - Cohorts 1, 2, and 4 (5-day Regimen)

			Primary Evaluation Part																		Extended Treatment Part		Withdrawal Examination[a]
			Course 1 (DLT Evaluation Period)[b]									Course 2 (Extended Treatment Period)						Course 3 and Subsequent Courses (Extended Treatment Period)				Extended Course		
	Screening		D1	D2	D3	D4	D5	D8	D15	D22	D29[c]	D1	D2-D5	D8	D15	D22	D29[c]	D1	D2-D5	D15	D29[c]	D1-D5	D29	Within 5 days after Withdrawal
Acceptable Time Window (Day)	−28	−14	1	2	3	4	5	6-10	12-18	19-25	26-32	1	2-5	6-10	12-18	19-25	26-32	1	2-5	12-18	26-32	1-5		
Written Consent[d]	○											○										○		
Patient Background Investigation	○																							
Investigation of Concomitant Drugs and Blood Transfusion[e]	←																				→	←	→	○
Investigation of AEs	←																				→	←	→	○
Medical Examination by Investigator or Subinvestigator (Subjective and Objective Findings)	○		○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Pregnancy Test (Urine or Serum Test)[f]		○									○													○
Viral Test[g]		○										○						○						
Verification of Eligibility, Enrollment		○																						
IMP Administration			↓	↓	↓	↓	↓					↓	↓					↓	↓			↓		
Vital Signs[h]		○	○	○	○	○	○	○	○	○	○	□	○	○	○	○	○	□	○	○	○			○
Height		○																						
Body Weight[i]			□								○	□						□						○
Twelve-lead ECG		○	□								○						○				○			○
Chest X-ray		○									○						○				○			○
Cardiac Function or Respiratory Function[j]		◊																						
Hematology Test[k]		○	□					○	○	○	○	□		○	○	○	○	□		○	○	□		○
Blood Biochemistry Test[l]		○	□								○	□					○	□			○			○
Urinalysis[m]		○	□								○	□					○	□			○			○

Schedule of Events (Refer to 7.1 Schedule and Procedures) - Cohorts 1, 2, and 4 (5-day Regimen)

		Primary Evaluation Part																			Extended Treatment Part		Withdrawal Examination[a]
		Course 1 (DLT Evaluation Period)[b]									Course 2 (Extended Treatment Period)						Course 3 and Subsequent Courses (Extended Treatment Period)				Extended Course		
	Screening	D1	D2	D3	D4	D5	D8	D15	D22	D29[c]	D1	D2-D5	D8	D15	D22	D29[c]	D1	D2-D5	D15	D29[c]	D1-D5	D29	Within 5 days after Withdrawal
Acceptable Time Window (Day)	−28 −14	1	2	3	4	5	6-10	12-18	19-25	26-32	1	2-5	6-10	12-18	19-25	26-32	1	2-5	12-18	26-32	1-5		
ECOG PS	○									○						○				○			○
Bone Marrow Aspiration[n]	○									○	←·····→						←·····→						○
Blood Sampling for PK[o]		○	○	○	○	○																	
Blood Sampling for PD[p]		○					○	○	○	○													
Evaluation of Efficacy[q]										○						○				○			○

○: Mandatory item
□: If such tests or examinations have already been conducted within 4 days before Day 1, those tests/examinations may be used as the Day 1 tests/examinations.
◊: Optional item related to inclusion criteria

[a] If the withdrawal examination is performed within the acceptable time window for Day 8, Day 15, Day 22, or Day 29, repeated tests/examinations are not necessary for those items already performed for the same day. If the discontinuation is due to a serious adverse event (SAE) or progression of disease, only those examinations that are feasible, given the subject's state of health, will be performed.

[b] Hospitalization during Course 1 is mandatory. For those subjects for whom the trial is concluded with Course 1, hospitalization until the withdrawal examination is mandatory. For those subjects who continue to receive IMP administration in Course 2 and subsequent courses, hospitalization until commencement of IMP administration in Course 2 is mandatory.

[c] If IMP administration for the next course is started from Day 29, the tests designated for Day 29 should be performed between Day 26 and before IMP administration on Day 32. (If the tests designated for Day 29 are performed within the acceptable time window, between Day 26 and Day 28, IMP administration for the next course will be started on or after Day 29.)

[d] Written consent at screening will be obtained prior to all observations, tests, examinations, and evaluations of this trial. Written consent for continuation of IMP administration in Course 2 and subsequent courses will be obtained before the start of Course 2 (after Day 22 administration of Course 1).

[e] Details on all concomitant medications taken from 28 days before the start of IMP administration until discontinuation will be collected. Information on any blood transfusions administered from 28 days before the start of IMP administration until 30 days after the last administration will also be collected. (If the subject starts another AML treatment or is transferred to another hospital, collection of such data will be continued up until that point.)

[f] To be performed for female subjects only. (However, a pregnancy test is not required for subjects who have undergone bilateral oophorectomy or hysterectomy, or subjects who have been amenorrheic without a medical cause for at least 12 consecutive months.)

[g] Human immunodeficiency virus antibody, HBV-DNA, hepatitis C virus (HCV) antibody, hepatitis B core antibody (HBcAB), and hepatitis B surface antibody (HBsAB) tests will be performed at screening. For those subjects who are found to be either HBcAB or HBsAB positive at screening, a test for HBV-DNA will be done on Day 1 in Course 2 and subsequent courses.

[h] Blood pressure (systolic/diastolic), pulse rate, body temperature (measured after the subject has rested in the sitting position for at least 3 minutes)

[i] Body weight will be measured and the dose of IMP to be administered will be determined according to the calculation of BSA.

[j] Cardiac function (echocardiography or multiple-gated acquisition [MUGA] scan) or respiratory function (DLCO or FEV 1) will be measured.

[k] Hemoglobin (Hb), hematocrit (Hct), red blood cell (RBC), white blood cell (WBC), differential WBC (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, promonocytes), platelet count, reticulocytes

[l] AST (glutamate oxaloacetate transaminase [GOT]), ALT (glutamate pyruvate transaminase [GPT]), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total protein (TP), albumin (ALB), T-Bil, blood urea nitrogen (BUN), uric acid (UA), Cr, blood glucose (fasting), Ca, Mg, Na, K, Cl

[m] Bilirubin, occult blood, protein, urobilinogen

[n] Bone marrow aspiration will be performed at screening and on Day 29 of Course 1. In Course 2 and subsequent courses, if peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed, bone marrow aspiration will be performed and the following items will be examined: percentage of bone marrow fluid (blasts, lymphoblasts, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, normoblasts, pronormoblasts, erythroblasts, plasma cells, and megakaryocytes), myeloid/erythroid ratio (M/E ratio), cellularity.
(If bone marrow aspiration has already been performed and any of the above items have been measured prior to acquisition of written informed consent and within the acceptable time window for the screening period [within 28 days before commencement of IMP administration], then those results can be used as the screening data, provided the subject's consent is obtained.)

[o] Blood sampling for PK:

Day 1 and Day 5: predose, 15 minutes, 30 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours after dosing
Day 2 (24 hours after Day 1 dosing), Day 3, and Day 4: predose (predose on Day 2 is the same as 24 hours postdose on Day 1)
[Acceptable time windows]

Day 1 and Day 5	predose:	Day 1: within 2 hours before IMP administration Day 5: ± 30 minutes of 24 hours from Day 4 dosing and before the Day 5 dosing
	15 minutes and 30 minutes postdose:	± 3 minutes
	60 minutes, 90 minutes, and 2 hours postdose:	± 6 minutes
	3 hours and 4 hours postdose:	± 12 minutes
	6 hours and 8 hours postdose:	± 24 minutes
	24 hours postdose:	± 30 minutes (24 hours postdose on Day 1 should be performed before Day 2 dosing)
Day 2, Day 3, Day 4	predose:	± 30 minutes of 24 hours from the previous dosing and before the dosing on that day

[p] Blood sampling for PD: blood sampling performed during screening is also acceptable for Day 1 sampling. If the sampling is performed on Day 1, it must be performed before dosing.

[q] In Course 2 and subsequent courses, evaluation of efficacy will be performed if peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed.

Schedule of Events (Refer to 7.1 Schedule and Procedures) - Cohort 3 (10-day Regimen): 10-day Regimen in Course 2 (Extended Treatment Period)

			Primary Evaluation Part																								Extended Treatment Part		Withdrawal Examination[c]
			Course 1 (DLT Evaluation Period)[a]											Course 2 (Extended Treatment Period)[b]										Course 3 and Subsequent Courses (Extended Treatment Period)				Extended Course		
	Screening		D1	D2	D3	D4	D5	D8	D9-11	D12	D15	D22	D29[d]	D1	D2	D3	D4	D5	D8	D9-12	D15	D22	D29[d]	D1	D2-D5	D15	D29[d]	D1-5	D29	Within 5 days after Withdrawal
Acceptable Time Window (Day)	−28	−14	1	2	3	4	5	8	9-11	12	13-18	19-25	26-32	1	2	3	4	5	8	9-12	13-18	19-25	26-32	1	2-5	12-18	26-32	1-5		
Written Consent[e]	○													○														○		
Patient Background Investigation	○																													
Investigation of Concomitant Drugs and Blood Transfusion[f]	←																						→					←	→	○
Investigation of AEs	←																						→					←	→	○
Medical Examination by Investigator or Subinvestigator (Subjective and Objective Findings)	○		○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Pregnancy Test (Urine or Serum Test)[g]		○											○																	○
Viral Test[h]		○												○										○						
Verification of Eligibility, Enrollment		○																												
IMP Administration			↓	↓	↓	↓	↓	↓	↓	↓				↓	↓	↓	↓	↓	↓	↓				↓	↓			↓		
Vital Signs[i]		○	○	○	○	○	○	○	○	○	○	○	○	□	○	○	○	○	○	○	○	○	○	□	○	○	○			○
Height		○																												
Body Weight[j]			□										○	□										□						○
Twelve-lead ECG		○	□										○										○				○			○
Chest X-ray		○											○										○				○			○

Schedule of Events (Refer to 7.1 Schedule and Procedures) - Cohort 3 (10-day Regimen): 10-day Regimen in Course 2 (Extended Treatment Period)

			Primary Evaluation Part																							Extended Treatment Part		Withdrawal Examination[c]
			Course 1 (DLT Evaluation Period)[a]											Course 2 (Extended Treatment Period)[b]										Course 3 and Subsequent Courses (Extended Treatment Period)				Extended Course		
	Screening		D1	D2	D3	D4	D5	D8	D9-11	D12	D15	D22	D29[d]	D1	D2	D3	D4	D5	D8	D9-12	D15	D22	D29[d]	D1	D2-D5	D15	D29[d]	D1-5	D29	Within 5 days after Withdrawal
Acceptable Time Window (Day)	−28	−14	1	2	3	4	5	8	9-11	12	13-18	19-25	26-32	1	2	3	4	5	8	9-12	13-18	19-25	26-32	1	2-5	12-18	26-32	1-5		
Cardiac Function or Respiratory Function[k]		◊																												
Hematology Test[l]		○	□					○			○	○	○	□					○		○	○	○	□		○	○	□		○
Blood Biochemistry Test[m]		○	□										○	□									○	□			○			○
Urinalysis[n]		○	□										○	□									○	□			○			○
ECOG PS		○											○										○				○			○
Bone Marrow Aspiration[o]		○											○	←·····→										←·····→						○
Blood Sampling for PK[p]			○	○			○			○																				
Blood Sampling for PD[q]			○					○			○	○	○																	
Evaluation of Efficacy[r]													○										○				○			○

Schedule of Events (Refer to 7.1 Schedule and Procedures) -Cohort 3 (10-day Regimen): 5-day Regimen in Course 2 (Extended Treatment Period)

			Primary Evaluation Part																				Extended Treatment Part		Withdrawal Examination[c]
			Course 1 (DLT Evaluation Period)[a]											Course 2 (Extended Treatment Period)[b]						Course 3 and Subsequent Courses (Extended Treatment Period)				Extended Course		
	Screening		D1	D2	D3	D4	D5	D8	D9 -11	D12	D15	D22	D29[d]	D1	D2 -5	D8	D15	D22	D29[d]	D1	D2- D5	D15	D29[d]	D1-5	D29	Within 5 days after Withdrawal
Acceptable Time Window (Day)	−28	−14	1	2	3	4	5	8	9-11	12	13-18	19-25	26-32	1	2-5	6-10	12-18	19-25	26-32	1	2-5	12-18	26-32	1-5		
Written Consent[e]	○													○										○		
Patient Background Investigation	○																									
Investigation of Concomitant Drugs and Blood Transfusion[f]			←										→										→	←	→	
Investigation of AEs			←										→										→	←	→	
Medical Examination by Investigator or Subinvestigator (Subjective and Objective Findings)	○		○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Pregnancy Test (Urine or Serum Test)[g]		○											○													○
Viral Test[h]		○												○						○						
Verification of Eligibility, Enrollment		○																								
IMP Administration			↓	↓	↓	↓	↓	↓	↓	↓				↓	↓					↓	↓			↓		
Vital Signs[i]		○	○	○	○	○	○	○	○	○	○	○	○	□	○	○	○	○	○	□	○	○	○			○
Height		○																								
Body Weight[j]			□										○	□						□						○
Twelve-lead ECG		○	□										○						○				○			○
Chest X-ray		○											○						○				○			○
Cardiac Function or Respiratory Function[k]		◊																								

Schedule of Events (Refer to 7.1 Schedule and Procedures) -Cohort 3 (10-day Regimen): 5-day Regimen in Course 2 (Extended Treatment Period)

			Primary Evaluation Part																				Extended Treatment Part		Withdrawal Examination[c]
			Course 1 (DLT Evaluation Period)[a]											Course 2 (Extended Treatment Period)[b]						Course 3 and Subsequent Courses (Extended Treatment Period)				Extended Course		
	Screening		D1	D2	D3	D4	D5	D8	D9 -11	D12	D15	D22	D29[d]	D1	D2 -5	D8	D15	D22	D29[d]	D1	D2- D5	D15	D29[d]	D1-5	D29	Within 5 days after Withdrawal
Acceptable Time Window (Day)	−28	−14	1	2	3	4	5	8	9-11	12	13-18	19-25	26-32	1	2-5	6-10	12-18	19-25	26-32	1	2-5	12-18	26-32	1-5		
Hematology Test[l]		○	□					○			○	○	○	□		○	○	○	○	□		○	○	□		○
Blood Biochemistry Test[m]		○	□										○	□					○	□			○			○
Urinalysis[n]		○	□										○	□					○	□			○			○
ECOG PS		○											○						○				○			○
Bone Marrow Aspiration[o]		○											○	←.....					→[d]	←.....			→[d]			○
Blood Sampling for PK[p]			○	○			○			○																
Blood Sampling for PD[q]			○					○			○	○	○													
Evaluation of Efficacy[r]													○						○				○			○

○: Mandatory item
□: If such tests or examinations have already been conducted within 4 days before Day 1, those tests/examinations may be used as the Day 1 tests/examinations.
◊: Optional item related to inclusion criteria

[a] Hospitalization during Course 1 is mandatory. For those subjects for whom the trial is concluded with Course 1, hospitalization until the withdrawal examination is mandatory. For those subjects who continue to receive IMP administration in Course 2 and subsequent courses, hospitalization until commencement of IMP administration in Course 2 is mandatory.

[b] Based on the subject's condition (the percentage of blasts in the peripheral blood and bone marrow, and peripheral blood cell counts) at the completion of Course 1, it will be determined whether or not the transition to Course 2 should be postponed and which regimen is used for each subject.

[c] If the withdrawal examination is performed within the acceptable time window for Day 15, Day 22, or Day 29, repeated tests/examinations are not necessary for those items already performed for the same day. If the discontinuation is due to a serious adverse event (SAE) or progression of disease, only those examinations that are feasible, given the subject's state of health, will be performed.

[d] If IMP administration for the next course is started from Day 29, the tests designated for Day 29 should be performed between Day 26 and before IMP administration on Day 32. (If the tests designated for Day 29 are performed within the acceptable time window, between Day 26 and Day 28, IMP administration for the next course will be started on or after Day 29.)

[e] Written consent at screening will be obtained prior to all observations, tests, examinations, and evaluations of this trial. Written consent for continuation of IMP administration in Course 2 and subsequent courses will be obtained before the start of Course 2 (after Day 22 administration of Course 1).

[f] Details on all concomitant medications taken from 28 days before the start of IMP administration until discontinuation will be collected. Information on any blood transfusions administered from 28 days before the start of IMP administration until 30 days after the last administration will also be collected. (If the subject starts another AML treatment or is transferred to another hospital, collection of such data will be continued up until that point.)

[g] To be performed for female subjects only. (However, a pregnancy test is not required for subjects who have undergone bilateral oophorectomy or hysterectomy, or subjects who have been amenorrheic without a medical cause for at least 12 consecutive months.)

[h] Human immunodeficiency virus antibody, HBV-DNA, hepatitis C virus (HCV) antibody, hepatitis B core antibody (HBcAB), and hepatitis B surface antibody (HBsAB) tests will be performed at screening. For those subjects who are found to be either HBcAB or HBsAB positive at screening, a test for HBV-DNA will be done on Day 1 in Course 2 and subsequent courses.

[i] Blood pressure (systolic/diastolic), pulse rate, body temperature (measured after the subject has rested in the sitting position for at least 3 minutes)

[j] Body weight will be measured and the dose of IMP to be administered will be determined according to the calculation of BSA.

[k] Cardiac function (echocardiography or multiple-gated acquisition [MUGA] scan) or respiratory function (DLCO or FEV 1) will be measured.

[l] Hemoglobin (Hb), hematocrit (Hct), red blood cell (RBC), white blood cell (WBC), differential WBC (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, promonocytes), platelet count, reticulocytes

[m] AST (glutamate oxaloacetate transaminase [GOT]), ALT (glutamate pyruvate transaminase [GPT]), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total protein (TP), albumin (ALB), T-Bil, blood urea nitrogen (BUN), uric acid (UA), Cr, blood glucose (fasting), Ca, Mg, Na, K, Cl

[n] Bilirubin, occult blood, protein, urobilinogen

[o] Bone marrow aspiration will be performed at screening and on Day 29 of Course 1. In Course 2 and subsequent courses, if peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed, bone marrow aspiration will be performed and the following items will be examined: percentage of bone marrow fluid (blasts, lymphoblasts, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, normoblasts, pronormoblasts, erythroblasts, plasma cells, and megakaryocytes), myeloid/erythroid ratio (M/E ratio), cellularity.
(If bone marrow aspiration has already been performed and any of the above items have been measured prior to acquisition of written informed consent and within the acceptable time window for the screening period [within 28 days before commencement of IMP administration], then those results can be used as the screening data, provided the subject's consent is obtained.)

[p] Blood sampling for PK:
Day 1 and Day 12: predose, 15 minutes, 30 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours after dosing
Day 5: 90 minutes, 6 hours after dosing
[Acceptable time windows]

Day 1 and Day 12	predose:	Day 1: within 2 hours before IMP administration Day 12: ± 30 minutes of 24 hours from Day 11 dosing and before the Day 12 dosing
	15 minutes and 30 minutes postdose:	± 3 minutes
	60 minutes, 90 minutes, and 2 hours postdose:	± 6 minutes
	3 hours and 4 hours postdose:	± 12 minutes

	6 hours and 8 hours postdose:	± 24 minutes
	24 hours postdose:	± 30 minutes (24 hours postdose on Day 1 should be performed before Day 2 dosing)
Day 5	90 minutes postdose:	± 6 minutes
	6 hours postdose:	± 24 minutes

[q] Blood sampling for PD: blood sampling performed during screening is also acceptable for Day 1 sampling. If the sampling is performed on Day 1, it must be performed before dosing.

[r] In Course 2 and subsequent courses, evaluation of efficacy will be performed if peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed.

Table of Contents

List of Abbreviations and Definition of Terms

List of Abbreviations

Abbreviation	Expansion
ADL	Activities of daily living
AE	Adverse event
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
APL	Acute promyelocytic leukemia
AST	Aspartate aminotransferase
BED	Biologically effective dose
BSA	Body surface area
BUN	Blood urea nitrogen
BW	Body Weight
CMML	Chronic myelomonocytic leukemia
Cr	Creatinine
CR	Complete remission
CRF	Case report form
CRi	Complete remission with incomplete blood count recovery
CRp	Complete remission with incomplete platelet recovery
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P-450
DLCO	Diffusing capacity of the lung for carbon monoxide
DLT	Dose-limiting toxicity
DNMT	DNA methyltransferase
ECG	Electrocardiogram, electrocardiography
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
FEV 1	Forced expiratory volume in the first second
GOT	Glutamate oxaloacetate transaminase
GPT	Glutamate pyruvate transaminase
GVHD	Graft-versus host disease
Hb	Hemoglobin
HBcAB	Hepatitis B core antibody
HBsAB	Hepatitis B surface antibody
HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin
Hct	Hematocrit
HCV	Hepatitis C virus
hERG	Human ether-a-go-go related gene
HI-E	Hematological improvement of erythrocytes
HI-P	Hematological improvement of platelets
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
ICF	Informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Abbreviation	Expansion
IMP	Investigational medicinal product
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
LINE-1	Long interspersed nucleotide element-1
LVEF	Left ventricular ejection fraction
M/E ratio	Myeloid/erythroid ratio
mCR	Marrow complete remission
MDS	Myelodysplastic syndrome
MTD	Maximum tolerated dose
MUGA	Multiple-gated acquisition
NE	Not evaluable
NOEL	No observed effect level
NYHA	New York Heart Association
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PR	Partial response
PS	Performance status
PT	Preferred term
QTc interval	Corrected QT interval
QTcF interval	QT interval as corrected by Fridericia's formula
RBC	Red blood cell
SAE	Serious adverse event
SC	Subcutaneous(ly)
SOC	System organ class
T-Bil	Total bilirubin
TP	Total protein
UA	Uric acid
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization

Definitions of Terms

Term	Definition
Screen failure	A screen failure is a subject from whom written informed consent is obtained, but to whom the investigational medicinal product (IMP) is not administered.
Individual subject trial start date	The day of obtaining the subject's written informed consent.
Withdrawn subject	A subject who withdraws from the trial during Course 1 without completing dose-limiting toxicity (DLT) evaluation or who withdraws from the trial after completing DLT evaluation. (Subjects who withdraw during Course 1, which is the DLT evaluation period, and those who withdraw after the DLT evaluation will be distinguished.)
Individual subject trial discontinuation date	The day of the withdrawal examination to be performed within 5 days from the day when the investigator or subinvestigator determines that the subject is to be withdrawn from the trial.
Completer	A subject who receives the specified IMP during Course 1, completes examinations, and is evaluable for DLTs.
Individual subject trial completion date	The day when the examination scheduled for Day 29 of Course 1 is performed or the start day of Course 2, whichever is later.
Individual subject trial period	A period from the day of obtaining the subject's informed consent to the day of trial discontinuation. Does not include the follow-up or outcome investigation period.

List of Pharmacokinetic Parameters

Abbreviation and Term (Unit)		Expansion or Definition
AUC_{∞}	ng·h/mL	Area under the plasma concentration-time curve from time zero to infinity
AUC_{∞}/D	ng·h/mL/mg/m^2	AUC_{∞} normalized by dose
AUC_{24h}	ng·h/mL	Area under the plasma concentration-time curve from time zero to 24 hours
AUC_{24h}/D	ng·h/mL/mg/m^2	AUC_{24h} normalized by dose
AUC_t	ng·h/mL	Area under the plasma concentration-time curve calculated to the last observable concentration at time t
AUC_t/D	ng·h/mL/mg/m^2	AUC_t normalized by dose
AUC_%Extrap	%	Percentage of AUC due to extrapolation from t_{last} to infinity ($[AUC_{\infty} - AUC_t] / AUC_{\infty} \times 100$)
CL/F	L/h, L/h/m^2	Apparent clearance of drug from plasma after extravascular administration, L/h normalized by body surface area (BSA)
CL/F/BW	L/h/kg	CL/F normalized in body weight
C_{max}	ng/mL	Maximum (peak) plasma concentration of the drug
C_{max}/D	ng/mL/mg/m^2	C_{max} normalized by dose
λ_z	h^{-1}	Apparent terminal-phase disposition rate constant (first-order)
$t_{1/2,z}$	h	Terminal-phase elimination half-life
t_{last}	h	Time of last measurable (positive) concentration
t_{max}	h	Time to maximum (peak) plasma concentration
V_z/F	L, L/m^2	Apparent volume of distribution during the terminal (λ_z) phase after extravascular administration, L normalized by BSA
$V_z/F/BW$	L/kg	V_z/F normalized in body weight
$R_{n,ac}$ (AUC_{24h})		Accumulation ratio of nth dose to first dose at regular administration for AUC_{24h}
$R_{n,ac}$ (C_{max})		Accumulation ratio of nth dose to first dose at regular administration for C_{max}

1 Introduction

1.1 Background of Trial Plan

SGI-110 is a dinucleotide incorporating decitabine, an inhibitor of DNA methylation, with deoxyguanosine via a phosphodiester bond. Decitabine (Dacogen®) has been approved and marketed in the United States (US) for the treatment of myelodysplastic syndrome (MDS) and in the European Union for the treatment of acute myeloid leukemia (AML) in elderly patients.[1]

DNA methylation is a conversion to 5-methylcytosine that occurs when cytosines in the CpG islands located in the gene promoter region are methylated, and this methylation regulates gene expression. It is believed that when DNA methylation occurs in the cancer suppressor gene promoter region, transcription of cancer suppressor genes is suppressed, which leads to cellular canceration. Since such DNA methylation is mediated by DNA methyltransferase (DNMT), a drug with DNMT inhibitory effect is expected to be effective against reduction in transcription activity of cancer suppressor genes and activation of cancer genes associated with DNA methylation by DNMT.

Decitabine is a typical drug with a DNMT inhibitory effect, and has been approved outside Japan as a treatment of AML and MDS owing to its DNA hypomethylation.

Decitabine is more quickly metabolized by cytidine deaminase. Since SGI-110 is a dinucleotide of decitabine and deoxyguanosine, it is cleaved into decitabine and deoxyguanosine. The cleaved decitabine is gradually released into plasma. Thus, plasma decitabine concentrations are maintained without acute elevation in plasma concentrations, resulting in prolonged exposure. Decitabine activity is S-phase dependent, and prolonged exposure is believed to result in increases in S-phase leukemia cells exposed to decitabine. Hence, SGI-110 is expected to be more effective than decitabine. Decitabine is assumed to form a covalent complex with DNMT, thereby directly inhibiting DNA synthesis. Nonclinical toxicity studies of decitabine have shown that increased exposure leads to cytotoxicity; therefore, the inhibition of DNA synthesis may be associated with an antitumor effect.

Acute myeloid leukemia is a highly diverse blood cancer characterized by clonal autonomous proliferation of immature bone marrow cells with impaired differentiation and/or maturation capacity. Abnormal proliferation of leukemia cells in the bone marrow results in marked inhibition of normal hematopoietic function, presenting various symptoms associated with decreased white blood cells (WBCs), anemia, and decreased platelets. Acute myeloid leukemia is a serious disease and would be fatal in a short

period of time because of infection or bleeding if not appropriately treated.[2] Among adult leukemias, AML is most frequent; the prevalence rate of AML in Japan is estimated to be approximately 2 to 4 per 100,000 population, and patients with AML account for approximately 55% to 65% of all patients with leukemia.[3,4,5] For the treatment of AML, an anthracycline (standard-dose idarubicin or high-dose daunorubicin) in combination with a standard dose of cytarabine is recommended as remission-induction therapy in patients with primary untreated AML.[2] This treatment achieves complete remission in approximately 80% of patients, but approximately 70% of these patients experience relapse. Also approximately 15% of patients show resistance to the first remission-induction therapy (poor responders to first therapy).[6] Many therapies have been attempted for these relapsed and treatment-resistant AMLs; however, no standard therapy has been established yet.[7]

For elderly patients with AML, a standard intensive chemotherapy, if tolerated, is expected to achieve a better remission rate and survival. However, it is difficult to uniformly perform chemotherapy with intensity equivalent to that for treatment-naïve younger patients with AML because of patients' characteristics such as decreased organ function. Furthermore, the incidence of adverse drug reactions is generally high when chemotherapy is given to elderly patients with AML, and adverse drug reactions are likely to be severe. Thus, the indication for a standard intensive chemotherapy needs to be carefully determined. When standard therapy is deemed to be inappropriate based on the performance status (PS), complications, and/or karyotypic abnormalities before the start of therapy, patients are treated with low-dose cytarabine if they are treatable. Its therapeutic results are however hardly adequate, and new drugs are therefore awaited.[2] Compared with intravenous decitabine, the pharmacokinetic (PK) profile of SGI-110 may be improved because of prolongation of exposure without acute elevation in plasma decitabine concentrations. Therefore, SGI-110 is assumed to more effectively treat elderly patients with AML.

As mentioned above, since SGI-110 has a better PK profile than that of intravenous decitabine, it may well be a novel drug for the treatment of elderly patients with AML and patients with relapsed or refractory AML for which no standard therapy has been established. Consequently, the sponsor has decided to develop SGI-110.

1.2 Study Results and Trial Rationale

1.2.1 Nonclinical Study Results

Results of nonclinical studies of SGI-110 are described below.

1.2.1.1 Pharmacology

Results of pharmacology studies using leukemia cell lines are described below.

In an in vitro study of SGI-110 added to HL60 and U937, human AML cell lines, and an in vivo study using severe combined immunodeficiency mice having U937 xenografted, subcutaneous (SC) administration of SGI-110 induced overall and gene-specific hypomethylation.

In a study using female nu/nu mice having HL60 cells grafted SC and receiving SGI-110 or decitabine SC or intraperitoneally, SC administration of SGI-110 showed an inhibitory effect on tumor growth similarly to decitabine. After intraperitoneal administration, the inhibitory effect of decitabine on tumor growth was stronger than that of SGI-110.

1.2.1.2 Safety Pharmacology

Cardiovascular system

The action of SGI-110 on the human ether-a-go-go related gene (hERG) potassium channel was investigated in vitro. Whole-cell patch clamp recording was done in human embryonic kidney (HEK 293) cells in which hERG cDNA was stably transfected. SGI-110 inhibited hERG current by 1.4 ± 0.3% (mean ± standard error of the mean) at 10 μM and by 1.0 ± 1.3% at 300 μM. The half maximal (50%) inhibitory concentration of SGI-110 for hERG current was not calculated but estimated to exceed 300 μM.

Central nervous system

In a repeated dose toxicity study in rats, the neurobehavioral toxicity of SGI-110 following the first SC administration (0, 5, 10, 20, or 30 mg/kg) was evaluated. Functional observational battery was used to observe 10 rats per dose group predose (Day −1) and 1 hour postdose on Day 1, and no SGI-110-related change was found in any of the groups. The no observed effect level (NOEL) of SGI-110 for neurobehavioral function was estimated to be 30 mg/kg, the maximum dose in this study.

Respiratory system

A single dose (0, 15, 30, or 60 mg/kg) of SGI-110 was administered SC to rats, and the respiratory functions (respiratory rate, tidal volume, and minute ventilation volume) were continuously monitored in 8 rats per group for at least 1 hour predose and at least 4 hours postdose. There was neither death attributable to SGI-110 nor effect on the general condition, respiratory rate, tidal volume, or minute ventilation volume. The NOEL of SGI-110 was estimated to be 60 mg/kg, the maximum dose in this study.

1.2.1.3 Toxicity

Repeated-dose toxicity studies were conducted in rats and rabbits. SGI-110 was administered SC once daily for 5 days with a 23-day recovery period provided. SGI-110 was administered at 5, 10, and 20 mg/kg/dose to rats and 1.5, 3.5, and 7.0 mg/kg/dose to rabbits. In both rats and rabbits, myelosuppression, hematotoxicity (decreases in WBCs, red blood cell [RBC] parameters, and platelet counts), and decreased thymus weight were observed at all of the doses. Toxicity findings partially or completely resolved after the recovery period. The no-observable-adverse-effect level was not identified for either of the animal species. The severely toxic dose in 10% in rats exceeded 20 mg/kg/dose (120 mg/m^2/dose), and the highest non-severely toxic dose (HNSTD) in rabbits was 1.5 mg/kg/dose (18 mg/m^2/dose). In a repeated-dose toxicity study with another dosing schedule (twice-weekly administration), spermatocyte/spermatid degeneration in the testes was reported.

In studies in cynomolgus monkeys, SGI-110 was administered SC once daily for 5 days (2.1 and 3 mg/kg/dose), once daily for 10 days (1.05 and 1.5 mg/kg/dose on Day 1 to Day 5 and Day 8 to Day 12), and twice weekly for 3 weeks (1.75 and 2.5 mg/kg/dose) over two 30-day cycles. Scabs were developed at the injection site. The scabs did not resolve and persisted until the end of the study. Body weight and food consumption were within normal limits. Other changes observed were decreased RBCs, increased platelet count, and decreased neutrophil count.

1.2.1.4 Genotoxicity and Mutagenicity

No study to evaluate the genotoxic or mutagenic potential of SGI-110 has been performed. Decitabine is a mutagenic substance.

1.2.1.5 Carcinogenicity

No study to evaluate the carcinogenic potential of SGI-110 has been performed. No carcinogenicity study of decitabine has been conducted.

1.2.1.6 Reproductive Toxicity

No study to evaluate the reproductive or developmental toxicity of SGI-110 has been conducted. Nonclinical toxicity studies in mice and rats have demonstrated that decitabine is teratogenic, fetotoxic, and embryotoxic.

1.2.1.7 Pharmacokinetics

There appeared to be pronounced differences among species in the PK profiles of SGI-110 and decitabine after SC administration. Conversion to decitabine occurred rapidly in rodents and rabbits but was slower in monkeys.

In terms of the PK of SGI-110, systemic exposure of SGI-110 decreased rapidly in rats and monkeys, and exposure of SGI-110 after repeated administration was dose-dependent in rats and rabbits.

The relative bioavailability of decitabine following SC administration of SGI-110 to rats was close to 100% in contrast to that following intravenous administration.

The concentrations of decitabine were high after SC administration of SGI-110 to mice, rats, and rabbits, but were much lower in monkeys. The systemic exposure of decitabine decreased rapidly. The exposure of decitabine after repeated administration of SGI-110 was dose-dependent in rats and rabbits.

In studies on metabolism, little metabolism was shown when SGI-110 was added to liver microsomes from various animals in vitro. Studies on the induction of metabolic enzymes revealed that SGI-110 does not strongly induce cytochrome P-450 (CYP) 1A1/2, CYP2C9, or CYP3A4 in human hepatocytes. Studies on the inhibition of metabolic enzymes demonstrated that SGI-110 does not have any CYP450 inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4.

Human plasma protein binding ratio of SGI-110 was low; in vitro unbound fraction was estimated to be 91%. Decitabine, the active ingredient, showed a very low protein binding ratio (< 1%).

After administration of radiolabeled decitabine, the mean cumulative urinary excretion rate of radioactivity was approximately 89.9% of the dose, and the mean cumulative fecal excretion rate of radioactivity was approximately 0.48% of the dose. In addition, the mean urinary excretion rate of decitabine was approximately 4.2% of the dose.

1.2.2 Clinical Study Results

Final databases for any clinical studies of SGI-110 have not been locked, and their clinical study reports (CSRs) have not been finalized.

The following sections describe clinical study results, mainly interim data from Study SGI-110-01 involving subjects with hematopoietic tumors.

1.2.2.1 Preliminary Results from Ongoing Clinical Studies

All results presented in this section are preliminary until the final study databases are locked and the CSRs are completed.

The clinical program of SGI-110 includes three ongoing phase 1/2 and phase 2 studies. As of the cutoff date on 26 Jul 2013, a total of 225 subjects have received at least one dose of SGI-110, and their data have been registered in the clinical study databases.

- SGI-110-01 phase 1 dose escalation study (monotherapy, enrollment completed, treatment ongoing) involved 93 patients.
- SGI-110-01 phase 2 extension study (monotherapy, enrollment ongoing) involved 108 patients.

1.2.2.1.1 Phase 1/2 Study: SGI-110-01 (AML/MDS; Monotherapy; United States and Canada)

A phase 1/2, dose escalation, multicenter study of two subcutaneous regimens of SGI-110, a DNA hypomethylating agent, in subjects with intermediate- or high-risk myelodysplastic syndrome or acute myeloid leukemia

Study SGI-110-01 is a first-in-human study involving subjects with MDS or AML and has been conducted with two regimens.

- The dose escalation segment (phase 1) is for determination of the biologically effective dose (BED) and maximum tolerated dose (MTD) using long interspersed nucleotide element-1 (LINE-1) data.
- The dose expansion segment (phase 2) is for evaluation of remission rates and safety in different subject populations (ie, MDS and AML).

These two segments are individually described below.

1.2.2.1.1.1 SGI-110-01 Phase 1 Dose Escalation Segment (AML/MDS; Monotherapy)

As of 26 Jul 2013, enrollment in the dose escalation segment has been completed, and treatment is ongoing.

The subjects enrolled in this segment had relapsed or refractory intermediate- or high-risk MDS (including chronic myelomonocytic leukemia [CMML]) or AML. The dose was escalated based on PK (area under the curve [AUC] for decitabine; see Section 1.2.2.1.2) and pharmacodynamic (PD) (hypomethylation in LINE-1; see Section 1.2.2.1.3) evaluations. Each cycle consisted of 28 days. The subjects were randomized to receive SGI-110 once daily for 5 days or once weekly for 3 weeks. Randomization to these two regimens was completed, and the study plan was modified to enroll subjects to receive SGI-110 twice weekly for 3 weeks (initial dose, 60 mg/m^2) because data of hypomethylation in LINE-1 showed that the 3-week once-weekly regimen was inferior.

The primary endpoint in this segment was to determine the BED and MTD. The MTD was decided based on the incidence of dose-limiting toxicities (DLTs) in Cycle 1. The safety profiles, PK profiles, and remission rates (hematological improvement and response duration) for SGI-110 and decitabine, and time to progression to AML (only in subjects with MDS) were also evaluated.

In the study database as of 26 Jul 2013, data from a total of 94 subjects in the dose escalation segment are available for analyses. SGI-110 was administered SC to 93 subjects (one subject was randomized to the 90 mg/m^2 once-weekly group but did not receive SGI-110). Of these, SGI-110 was administered to 44 subjects once daily for 5 days (3 to 125 mg/m^2), 34 subjects once weekly for 3 weeks (6 to 125 mg/m^2), and 15 subjects twice weekly for 3 weeks (60 or 90 mg/m^2).

SGI-110 was administered SC to the majority of subjects (67%) for 2 cycles. SGI-110 was administered SC to 46%, 28%, 18%, and 14% of the subjects for 3, 4, 5, and 6 cycles, respectively. The actual number of cycles was similar among the regimens.

Activity/efficacy of SGI-110

The following clinical effects were noted in the phase 1 dose escalation segment (63 subjects with AML and 15 subjects with MDS):

- AML (Kantarjian, et al[8]):
  - Complete remission (CR) was achieved in 5 subjects out of the subjects with AML who had previously received many therapies: ie, CR in 2 subjects, complete remission with incomplete platelet recovery (CRp) in 1 subject, and complete remission with incomplete blood count recovery (CRi) in 2 subjects were achieved with the 5-day once-daily regimen at the initial dose of 36 mg/m^2 and the once-weekly regimen at the initial dose of 60 mg/m^2.
  - No clinical remission was achieved with the twice-weekly regimen (11 subjects received this regimen).
  - The median duration of remission or CR was 114 days (ranging from 42 to 558 days).
- MDS (O'Connell, et al[9] and in-house document):
  - Remission was achieved in 7 subjects out of the subjects with MDS who had previously received many therapies: ie, marrow complete remission (mCR) in 2 subjects, hematological improvement of erythrocytes (HI-E) in 2 subjects, HI-E/hematological improvement of neutrophils in 1 subject, and HI-E/hematological improvement of platelets (HI-P) in 1 subject were achieved with the 5-day once-daily regimen at the initial dose of 18 mg/m^2 (remission achieved in 2 subjects) and the once-weekly regimen at the initial dose of 6 mg/m^2 (remission achieved in 4 subjects). HI-P in 1 subject with CMML was achieved with the twice-weekly regimen at the initial dose of 60 mg/m^2.
  - The median duration of remission or CR was 88 days (ranging from 77 to 181 days).

DNA hypomethylation in LINE 1 exceeding 10% was demonstrated in all of the AML subjects with remission and all of the MDS subjects with mCR.

Safety

Maximum tolerated dose

In the study, 5 DLTs (thrombocytopenia, neutropenia, febrile neutropenia, and sepsis) occurred in 2 subjects (both with MDS) treated with the 5-day once-daily regimen at 125 mg/m^2. No DLT occurred in the subjects with AML.

Therefore, the MTD for the 5-day once-daily regimen in the subjects with MDS was 90 mg/m^2. No MTD was reached for the 5-day once-daily regimen in the subjects with AML, or the once-weekly regimen or the twice-weekly regimen. The highest dose administered was 125 mg/m^2 for the 5-day once-daily regimen and the once-weekly regimen, and 90 mg/m^2 for the twice-weekly regimen.

Serious adverse events (safety database as of 04 Sep 2013)

Overall, serious adverse events (SAEs) occurred in 71 of the 93 subjects (76%). The majority of SAEs were assessed as unrelated to the investigational medicinal product (IMP) by the investigator or subinvestigator.

In addition, SAEs resulting in death occurred in 17 of the 93 subjects (18%). In 2 subjects, SAEs (sepsis in both) resulting in death were assessed as related to the IMP by the investigator or subinvestigator. One of these subjects was treated with the 5-day once-daily regimen at a low dose of 18 mg/m^2, and the SAE was assessed as unrelated by the sponsor. The other subject was treated with the 5-day once-daily regimen at 125 mg/m^2, and the SAE was assessed as related by the sponsor.

The system organ class (SOC) with the most frequently reported SAEs was infections and infestations (49%), followed by blood and lymphatic system disorders (34%).

The most frequently reported SAEs were febrile neutropenia (34%), pneumonia (23%), and sepsis (11%). Serious adverse events related to the IMP occurred in 7 of the 93 subjects (18%), including febrile neutropenia (5%), sepsis (3%), thrombocytopenia (1%), atrial fibrillation (1%), dysphagia (1%), chest pain (1%), mucosal inflammation (1%), bacteraemia (1%), Klebsiella sepsis (1%), pneumonia (1%), pneumonia klebsiella (1%),

platelet count decreased (1%), pseudomonal sepsis (1%), delirium (1%), and pleural effusion (1%).

Adverse events (clinical database as of 26 Jul 2013)

Adverse events (AEs) occurred in 92 of the 93 subjects (99%). The most frequently reported AEs were febrile neutropenia (43%), diarrhoea (37%), pneumonia (30%), injection site pain (29%), fatigue (28%), thrombocytopenia (26%), cough (24%), anaemia (23%), and dyspnoea (22%). The SOCs with the most frequently reported Grade 3 or worse AEs were blood and lymphatic system disorders (69%), and infections and infestations (49%).

Adverse events related to the IMP occurred in 63 of the 93 subjects (68%). The most frequently reported IMP-related AEs were injection site pain (29%), thrombocytopenia (14%), fatigue (13%), anaemia (12%), and neutropenia (11%). The SOC with the most frequently reported Grade 3 or worse IMP-related AEs was blood and lymphatic system disorders (30%).

1.2.2.1.1.2 SGI-110-01 Phase 2 Dose Expansion Segment (AML/MDS; Monotherapy)

As of 26 Jul 2013, enrollment in the dose expansion segment is ongoing.

This segment was implemented as a phase 2 randomized, extension study and evaluated subjects with the following four diseases:

- Relapsed or refractory AML
- Relapsed intermediate-2 or high-risk MDS (including CMML) previously treated with a hypomethylating agent
- Treatment-naïve AML in elderly subjects (aged 65 years or older)
- Treatment-naïve MDS (including CMML)

In the study, the subjects were randomized to receive either 60 or 90 mg/m^2 once daily for 5 days (one dose a day 5 times). Thereafter, the protocol was revised to add a fifth treatment group, consisting of non-randomized subjects receiving 60 mg/m^2 once daily for 10 days (subjects with relapsed or refractory AML only).

The primary endpoint of the phase 2 study was an overall remission rate (CR, CRp, and CRi) assessed using criteria of an international working group. A PD action for DNA methylation in LINE-1 was also evaluated.

In the study database as of 26 Jul 2013, data from a total of 109 subjects in the phase 2 dose expansion segment are available for analyses. SGI-110 was administered to 108 subjects (one subject was randomized but did not receive SGI-110).

Overall, SGI-110 was administered SC in the majority of subjects (78%) for 2 cycles. SGI-110 was administered SC to 51%, 31%, 19%, and 10% of the subjects for 3, 4, 5, and 6 cycles, respectively.

Efficacy

As of 26 Jul 2013, data from 50 subjects with relapsed or refractory AML and 17 elderly subjects with treatment-naïve AML are available. For the overall remission rate (CR, CRp, or CRi) defined as the primary endpoint, remission was achieved as described below:

- Of the 50 subjects with relapsed or refractory AML, complete remission (CR, CRp, or CRi) was achieved in 8 subjects (16%).
- Of the 17 elderly subjects with treatment-naïve AML, complete remission (CR, CRp, or CRi) was achieved in 9 subjects (53%).
- Five subjects (4 subjects with relapsed or refractory AML and 1 elderly subject with treatment-naïve AML) underwent stem cell transplantation after SGI-110 treatment.

There was no difference in the complete remission rate between the 60 and 90 mg/m^2 doses (remission was achieved in 8 of 32 subjects at 60 mg/m^2 and in 9 of 35 subjects at 90 mg/m^2). Data of DNA methylation in LINE-1 before and after treatment were available from 50 subjects (75%). DNA hypomethylation in LINE-1 by at least 10% was noted after treatment in 83% and 78% of the subjects in the 60 and 90 mg/m^2 groups, respectively. The median maximal hypomethylation in LINE-1 was 25% in the subjects with remission and 19% in the subjects without remission.

No efficacy data have been obtained from the subjects with treatment-naïve or relapsed or refractory MDS or the subjects with relapsed or refractory AML treated with the 10-day regimen at the time of data cutoff on 26 Jul 2013.

Safety

Serious adverse events (safety database as of 04 Sep 2013)

Serious adverse events occurred in 143 of the 216 subjects (66%). The majority of SAEs were assessed as unrelated to the IMP by the investigator or subinvestigator.

In addition, SAEs resulting in death occurred in 14 of the 216 subjects (6%). None of the SAEs resulting in death in the phase 2 dose expansion segment were assessed as related to the IMP.

The SOC with the most frequently reported SAEs was blood and lymphatic system disorders (41%), followed by infections and infestations (30%).

The most frequently reported SAEs were febrile neutropenia (37%) and pneumonia (13%).

Serious adverse events related to the IMP occurred in 25 of the 216 subjects (12%), including febrile neutropenia (7%), pneumonia (1%), anaemia (< 1%), thrombocytopenia (< 1%), diarrhoea (< 1%), nausea (< 1%), oesophagitis (< 1%), small intestinal obstruction (< 1%), chest pain (< 1%), fatigue (< 1%), pyrexia (< 1%), bronchopulmonary aspergillosis (< 1%), cellulitis (< 1%), escherichia bacteraemia (< 1%), pseudomonal bacteraemia (< 1%), sepsis (< 1%), staphylococcal sepsis (< 1%), upper respiratory tract infection (< 1%), hyperuricaemia (< 1%), tumour lysis syndrome (< 1%), and hypoxia (< 1%).

Adverse events (clinical database as of 26 Jul 2013)

Adverse events occurred in 92 of 108 subjects (85%). The most frequently reported AEs were febrile neutropenia (39%), injection site pain (31%), thrombocytopenia (25%), diarrhoea (25%), anaemia (23%), hypokalaemia (23%), neutropenia (22%), nausea (22%), and fatigue (21%). The SOCs with the most frequently reported Grade 3 or worse AEs were blood and lymphatic system disorders (62%), and infections and infestations (31%).

Adverse events related to the IMP occurred in 71 of the 108 subjects (66%). The most frequently reported IMP-related AEs were injection site pain (30%), neutropenia (19%), thrombocytopenia (19%), anaemia (17%), febrile neutropenia (13%), leukopenia (15%), diarrhoea (14%), nausea (14%), fatigue (12%), and constipation (11%). The SOC with the most frequently reported Grade 3 or worse IMP-related AEs was blood and lymphatic system disorders (37%).

1.2.2.1.2 Pharmacokinetics in Study SGI-110-01

Study SGI-110-01 was conducted to investigate the PK profiles of SGI-110 and decitabine following SC administration of SGI-110 with the 5-day once-daily regimen (3 to 125 mg/m^2), 3-week once-weekly regimen (6 to 125 mg/m^2), and 3-week twice-weekly regimen (60 or 90 mg/m^2). As a result, SGI-110 and decitabine were detected in the plasma of the subjects at all the dose levels of the 3 regimens. Decitabine exposure

was prolonged with the dose increase, and decitabine was detected continuously for at least 8 hours when the dose of SGI-110 was 18 mg/m^2 or higher. SGI-110 or decitabine was not detectable in the plasma 24 hours after administration of SGI-110, and no accumulation was noted. There was no PK difference between the 5-day once-daily regimen and 3-week once-weekly regimen.

SGI-110 and decitabine exposures after SC administration of SGI-110 were evaluated based on the AUC. The AUCs for both SGI-110 and decitabine increased dose proportionally, and the exposure increased. The C_{max} of SGI-110 or decitabine was not dose proportional. The $t_{1/2}$ of decitabine was prolonged after SC administration of SGI-110 (up to 2 hours), compared with that after intravenous administration of decitabine (0.25 to 0.58 hours). The mean AUCs for decitabine after SC administration of SGI-110 at 60, 90, and 125 mg/m^2 were, respectively, 0.77, 1.26, and 2.01 times the estimated therapeutic range (115 ng·h/mL) after 1-hour intravenous administration of decitabine 20 mg/m^2. The mean values of C_{max} were, respectively, 0.18, 0.29, and 0.44 times the range; therefore showing lower values than those after intravenous administration of decitabine.

1.2.2.1.3 Pharmacodynamics in Study SGI-110-01

Overall DNA methylation in long interspersed nucleotide element-1

DNA hypomethylation in LINE-1 was enhanced dose-dependently in subjects who received SGI-110 with the 5-day once-daily regimen at a dose range of 18 to 60 mg/m^2; the BED for the 5-day once-daily regimen was deemed to be 60 mg/m^2 since the maximum average DNA hypomethylation reached a plateau (up to 25%) at higher doses (90 to 125 mg/m^2).

Hypomethylation for the 3-week twice-weekly regimen reached a plateau of up to 18% at a dose range of 60 to 90 mg/m^2.

The extent of hypomethylation for the 3-week once-weekly regimen was lower than that for the 5-day once-daily regimen in all the cohorts.

Hypomethylation at doses of 60 and 90 mg/m^2 in the 3 regimens was compared. The results showed that the duration of hypomethylation in LINE-1 was longer for the 3-week twice-weekly regimen than for the 5-day once-daily regimen, whereas the extent of hypomethylation was more potent for the 5-day once-daily regimen. The extent of hypomethylation was weaker and the duration of hypomethylation was shorter for the 3-week once-weekly regimen than for the other two regimens.

1.2.3 Trial Rationale

This clinical trial will be conducted to evaluate the tolerability of SGI-110 in Japanese patients with AML. The target population, doses, and regimens were chosen with reference to a clinical trial (Study SGI-110-01) conducted outside of Japan in patients with AML and patients with MDS.

The target population will be patients with AML since the patients who responded to treatment to a certain extent in Study SGI-110-01 were those with AML. Also, in accordance with the Guidelines for Clinical Evaluation of Antimalignant Tumor Drugs (dated 01 Nov 2005), it was decided to select patients who are unlikely to achieve life prolongation or symptom relief with the generally accepted standard regimen, ie, patients who have relapsed after standard therapy, patients who do not respond to standard therapy, and elderly patients aged 65 years or older who are not eligible for standard chemotherapy.

The doses selected for the trial were based on the results of a clinical trial conducted outside of Japan (Study SGI-110-01). In Study SGI-110-01, the initial dose was set as 3 mg/m^2 per time (15 mg/m^2 per course) with a 5-day regimen, since this is one-sixth of the HNSTD (18 mg/m^2/time) for rabbits, the most sensitive species. The dose was increased to 6 mg/m^2 (30 mg/m^2 per course), 18 mg/m^2 (90 mg/m^2 per course), 36 mg/m^2 (180 mg/m^2 per course), 60 mg/m^2 (300 mg/m^2 per course), 90 mg/m^2 (450 mg/m^2 per course), and 125 mg/m^2 (625 mg/m^2 per course) with safety monitored. As a result, no DLT was observed at a dose range of up to 90 mg/m^2; a good tolerability profile was shown. In contrast, DLTs occurred in 2 of 3 patients with MDS who received a dose increased to 125 mg/m^2 (625 mg/m^2 per course). Thus, the MTD was determined to be 90 mg/m^2. A 3-week once-weekly regimen was also explored at an initial dose of 6 mg/m^2 (18 mg/m^2 per course), which is one-sixth of the dose well tolerated in rabbits (36 mg/m^2/time). The dose was increased up to 125 mg/m^2 (375 mg/m^2 per course), but the MTD was not reached.

A PD analysis to examine the BED indicated that a maximum of approximately 25% DNA hypomethylation in LINE-1 was achieved at doses of 60, 90, and 125 mg/m^2 of the 5-day once-daily regimen, and no great difference in the extent of hypomethylation. Thus, the BED was suggested to be 60 mg/m^2. In the 3-week once-weekly regimen, the extent of hypomethylation was low at all of the dose levels, and it was decided to implement the dose expansion segment for the phase 2 part with a 5-day once-daily regimen.

Efficacy was explored with the doses and regimens suggested to be the MTD and BED in the dose expansion segment implemented for the phase 2 part of Study SGI-110-01. The results revealed that composite complete remission was achieved in 16% of subjects with AML receiving SGI-110 at 60 and 90 mg/m^2 who had relapsed after standard therapy or had not responded to treatment and in 53% of elderly patients with treatment-naïve AML who were not eligible for standard chemotherapy, suggesting that 60 and 90 mg/m^2 were effective doses (as of 26 Jul 2013).

As mentioned above, the doses for the trial were chosen based on evaluations of the safety, efficacy, and PD of SGI-110 in a clinical trial conducted outside of Japan (Study SGI-110-01), and it was decided to adopt a study design to evaluate the tolerability in each cohort and gradually escalate the dose.

Since the results of Study SGI-110-01 suggest that the recommended dose for non-Japanese patients is assumed to be 60 mg/m^2, the primary dose to be investigated has been set as 60 mg/m^2. This study is the first clinical trial of SGI-110 involving Japanese patients with AML and, therefore, in considering the subjects' safety, the initial dose will be 36 mg/m^2, which was one of the doses used in Study SGI-110-01 and is a lower dose than the primary dose of 60 mg/m^2. The maximum dose will be 90 mg/m^2, which was determined to be the MTD in Study SGI-110-01 and is suggested to be effective according to exploratory evaluation.

In 2014, SGI-110 at 60 mg/m^2 in a 5-day regimen was chosen as a dose and regimen for the multi-national phase 3 trial (Study SGI-110-04) in treatment-naïve patients with AML who were ineligible for intensive chemotherapy. Therefore, this protocol was amended to version 3 on 22 May 2015 to exclude Cohort 3 (60 mg/m^2 in 10-day regimen) from the design. As of Aug 2016, Study SGI-110-04 was still ongoing in Japan. Then, another multi-national phase 3 trial (Study SGI-110-06) in patients with relapsed or refractory AML was newly planned in 2016. Based on the results of the phase 2 segment of Study SGI-110-01 in patients with relapsed or refractory AML (refer to IB for the data), the initial dose of Study SGI-110-06 was set as 60 mg/m^2 daily for 10 days. To evaluate the tolerability of the dosage (60 mg/m^2 in 10-day regimen) in Japanese patients before Study SGI-110-06 starts in Japan, this protocol was amended to version 6 on 05 Sep 2016 to reinstate Cohort 3 into the design.

As mentioned in Section 1.2.2 Clinical Study Results, occurrences of myelosuppression and decreased blood cell counts, and infections attributable to these, as well as occurrences of digestive symptoms are anticipated following administration of SGI-110.

Therefore subjects will be hospitalized during Course 1, when the IMP will be administered for the first time to them, so they can be carefully monitored. Thereafter, the subjects are to visit the trial site at least once weekly to undergo hematological tests for evaluation of decreased blood cell counts and to undergo a medical examination by a physician to check their general condition. In addition, a chest X-ray examination and blood biochemistry test are to be performed before the start of the next course in order to ensure the subjects' safety.

The subjects for the clinical trial are expected to have symptoms that may affect activities of daily living (ADL) such as decreased blood cell counts and infection associated with the progression of disease already present at study entry. Hence, supportive care used in routine medical practice is to be permitted, and arrangements will be made to prevent the subjects' quality of life from being undermined by participation in the trial.

As described the above, the trial has been planned so as to adequately ensure the subjects' safety. The conduct of the trial based on this protocol is judged to be scientifically and ethically appropriate.

See the investigator's brochure for further details of data mentioned in this protocol and other trial results.

2 Trial Objectives

2.1 Primary Objective

To evaluate the tolerability of SGI-110 when administered subcutaneously to Japanese patients with AML

Secondary objectives:

- To perform PK evaluation of plasma SGI-110 and decitabine
- To evaluate efficacy (complete remission rate, composite complete remission rate, overall remission rate, overall survival, composite complete remission duration)
- To evaluate safety through observed AEs and examinations

Exploratory objective:

To perform PD evaluation of the extent of DNA hypomethylation

3 Trial Plan

3.1 Trial Design

This is a phase 1, multicenter, open-label study to evaluate the tolerability of SGI-110 in Japanese patients with relapsed or refractory AML after undergoing standard therapy or Japanese patients with AML aged 65 years or older who are not eligible for standard chemotherapy.

This trial consists of a screening period, DLT evaluation period, and withdrawal examination. Subjects who complete IMP administration and all observations during the DLT evaluation period, and who do not have any apparent progression of AML, will be permitted to continue treatment with IMP following the DLT evaluation period if they wish. The primary evaluation data for Cohorts 1, 2, and 4 will have a cutoff date of 31 May 2016 and the data for Cohort 3 will have a cutoff date of 30 Nov 2017. The period up until the data cutoff will be defined as the primary evaluation part. This will be followed by an extended treatment part to assess long-term safety, which will include those subjects on IMP treatment who have consented to participate in the extended treatment part. Transition from the primary evaluation part to the extended treatment part will take place at the start of the next course after the data cutoff.

Administration of the IMP will be started in Cohort 1 (36 mg/m^2 in 5-day regimen) and 3 subjects will receive the IMP in this cohort. If none of the 3 subjects has a DLT during the DLT evaluation period, the study will proceed to the next cohort. If one of the 3 subjects experiences a DLT, 3 additional subjects will be enrolled and DLTs will be evaluated in a total of 6 subjects. The study will proceed to the next cohort only if no more than one of the 6 subjects has a DLT. If the number of subjects exhibiting a DLT within a cohort is $\geq 2/3$ or $\geq 2/6$, there will be no dose escalation.

In Cohort 2 (60 mg/m^2 in 5-day regimen) and Cohort 4 (90 mg/m^2 in 5-day regimen), DLTs will be assessed in the same manner. However, even if none of the first 3 subjects enrolled has a DLT, a total of 6 subjects will be enrolled in each of Cohorts 2 and 3 of which the dose has been determined as the recommended dose for a next phase study.

Based on the occurrence of DLTs, the tolerability at the recommended dose for a next phase study will be confirmed in Japanese subjects as well.

The sponsor will review safety data obtained from the previous cohort(s) and judge the transition to the next cohort, including selection of a cohort to proceed to, based on the advice of the Independent Data Monitoring Committee.

If the number of subjects exhibiting DLT within a cohort is ≥ 2/3 or ≥ 2/6, then there will be no transition to the next cohort, and the MTD will be determined as follows:

≥ 2/3 or ≥ 2/6 subjects with DLT	MTD
In Cohort 1	< 36 mg/m^2 in 5-day regimen
In Cohort 2	36 mg/m^2 in 5-day regimen
In Cohort 4	60 mg/m^2 in 5-day regimen

If the incidence of DLT does not reach either ≥ 2/3 or ≥ 2/6 in any of the cohorts in the table above, the MTD will not be determined in this study. For Cohort 3 (60 mg/m^2 in 10-day regimen), DLT will be evaluated but the MTD of 10-day regimen will not be determined from the incidence of DLT.

The DLT evaluation period will be from the start of administration in Course 1 to the examination scheduled for Day 29 of Course 1. However, for subjects who have postponed the start of IMP administration scheduled for Day 1 of Course 2 (extended treatment period), the DLT evaluation period will last until the start of IMP administration in Course 2.

Subjects will be hospitalized for treatment during Course 1. Subjects will be required to remain hospitalized until the examination scheduled for Day 29 of Course 1 if they complete the trial in Course 1 (until the withdrawal examination if they are withdrawn during Course 1) and until the start of IMP administration in Course 2 if they proceed to the extended treatment period of Course 2 and the subsequent courses.

Dose-limiting toxicity shall be defined as any of the following AEs occurring during Course 1 for which there is a reasonable probability or possibility of a causal relationship with the IMP (being related to the IMP) if it cannot be reasonably explained by underlying disease, intercurrent illness, or concomitant medications. The severity of AEs will be graded in accordance with Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

- Non-hematologic toxicity of Grade 3 or higher, except for the following:
  - Nausea, vomiting, or diarrhea of Grade 3 that is controllable by optimal therapy
  - Grade 3 laboratory findings other than serum creatinine (Cr), bilirubin, aspartate aminotransferase (AST), or alanine aminotransferase (ALT), that are not associated with clinical manifestations
- Grade 4 thrombocytopenia that was not present at study entry and that is not resolved within 7 days
- Grade 4 neutropenia that was not present at study entry and that is not resolved within 7 days

- Febrile neutropenia [Note]

  If the febrile neutropenia is not resolved or improved during the DLT evaluation period, it shall be defined as DLT. If the febrile neutropenia is resolved or improved during the DLT evaluation period, it shall be judged whether it is defined as DLT based on the background of the subject and through consultation with the Independent Data Monitoring Committee.
- Any AE that results in a delay of > 4 weeks in starting the next treatment course

[Note] In this trial, febrile neutropenia is defined as a neutrophil count of < 500/μL accompanied by a fever of ≥ 38°C

The DLT evaluation period will be for the duration of Course 1. Subjects who complete IMP administration and all observations during the DLT evaluation period, and who do not have any apparent progression of AML, will be permitted to continue treatment with IMP following the DLT evaluation period if they wish.

3.2 Rationale for Trial Design

In the trial, the dose escalation was planned with consideration of the subjects' safety and based on the "Guidelines for Clinical Evaluation of Antimalignant Tumor Drugs (Notification No. 1101001 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau dated 01 Nov 2005)."

As mentioned in Section 1.2.3 Trial Rationale, the doses and regimen were chosen based on evaluations of the safety, efficacy, and PD of SGI-110 in a clinical trial conducted outside of Japan (Study SGI-110-01), and it has been decided to adopt a study design to evaluate the tolerability in each cohort and gradually escalate the dose.

Since results of Study SGI-110-01 suggest that the recommended dose for non-Japanese patients is assumed to be 60 mg/m^2, the primary dose to be investigated has been set as 60 mg/m^2. This study is the first clinical trial of SGI-110 involving Japanese patients with AML and, therefore, in considering the subjects' safety, the initial dose will be 36 mg/m^2, which was one of the doses used in Study SGI-110-01 and is a lower dose than the primary dose of 60 mg/m^2. The maximum dose will be 90 mg/m^2, which was determined to be the MTD in Study SGI-110-01 and is suggested to be effective according to exploratory evaluation. In addition, the tolerability of SGI-110 at 60 mg/m^2 once daily for 10 days will be evaluated in Japanese patients in this study because the same dose and regimen is planned to be adopted in Study SGI-110-06 in patients with relapsed or refractory AML.

As mentioned in Section 1.2.2 Clinical Study Results, occurrences of myelosuppression and decreased blood cell counts, and infections attributable to these, as well as

occurrences of digestive symptoms are anticipated following administration of SGI-110. Therefore subjects will be hospitalized during Course 1, when the IMP will be administered for the first time to them, so they can be carefully monitored. Thereafter, the subjects are to visit the trial site at least once weekly to undergo hematological tests for evaluation of decreased blood cell counts and to undergo a medical examination by a physician to check their general condition. In addition, a chest X-ray examination and blood biochemistry test are to be performed before the start of the next course in order to ensure the subjects' safety.

The subjects for the clinical trial are expected to have symptoms that may affect ADL such as decreased blood cell counts and infection associated with the progression of disease already present at study entry. Hence, supportive care used in routine medical practice is to be permitted, and arrangements will be made to prevent the subjects' quality of life from being undermined by participation in the trial.

The subjects for the trial will be patients who have relapsed after existing therapy or do not respond to treatment, and elderly patients aged 65 years or older who are not eligible for standard intensive chemotherapy; therefore they have limited treatment options. For ethical reasons, a subject will be allowed to continue with the IMP after the completion of the DLT evaluation period if they wish to do so as long as they have not experienced an AE during Course 1 (ie, the DLT evaluation period of the trial) that makes continuing the IMP difficult and have no evidence of disease progression. Safety and efficacy will be continuously evaluated during the primary evaluation part. For long-term safety evaluation after the end of the primary evaluation part, an extended treatment part will be included so that treatment can be continued for subjects who are on the IMP at that time if they consent to continue the treatment.

3.3 Endpoints

3.3.1 Safety

3.3.1.1 Primary Endpoint (Primary Evaluation Part)

DLT

3.3.1.2 Secondary Endpoints

(Primary evaluation part)

AEs, clinical laboratory values, vital signs (blood pressure, pulse rate, body temperature), body weight, Eastern Cooperative Oncology Group (ECOG) PS, 12-lead electrocardiogram (ECG), chest X-ray

(Extended treatment part)

AEs, clinical laboratory values

3.3.2 Efficacy Endpoints (Primary Evaluation Part)

Complete remission rate (CR), composite complete remission rate (CR + CRi + CRp), overall remission rate (CR + CRi + CRp + partial response [PR]), overall survival, and composite complete remission duration

3.3.3 Pharmacokinetic Endpoints (Primary Evaluation Part)

SGI-110 and decitabine plasma concentrations, PK parameters

3.3.4 Pharmacodynamic Endpoint (Primary Evaluation Part)

Extent of DNA hypomethylation in LINE-1

[Rationale for variable selection]

[Safety]

Safety in each cohort is to be evaluated in accordance with the "Guidelines for Clinical Evaluation of Antimalignant Tumor Drugs" (Notification No. 1101001 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau dated 01 Nov 2005). DLTs and AEs are to be assessed using the criteria used for toxicity assessment of other anticancer drugs (CTCAE version 4.0 of the US National Cancer Institute).

[Efficacy]

Efficacy is to be evaluated in accordance with the criteria used in a phase 1/2 trial conducted outside of Japan (Study SGI-110-01) which was a partially modified version of the response criteria for AML treatment established by an international working group.[10]

[Pharmacokinetics]

SGI-110 and decitabine plasma concentrations in Japanese subjects are to be measured to evaluate PK parameters.

[Pharmacodynamics]

The extent of DNA hypomethylation, which is regarded as the main action of SGI-110, is to be measured.

3.4 Target Number of Patients

Maximum: 24 subjects

Cohort 1 (36 mg/m^2, 5 days): 3 to 6 subjects

Cohort 2 (60 mg/m^2, 5 days): 3 to 6 subjects

Cohort 3 (60 mg/m^2, 10 days [ie, 5-day administration twice, with a non-dosing period in-between]): 6 subjects

Cohort 4 (90 mg/m^2, 5 days): 3 to 6 subjects

3.5 Rules to Be Observed for Enrollment and Treatment

1) The dose or regimen should remain unchanged for each subject, and no subject should be re-enrolled.
2) In order to avoid occurrence of unexpected serious adverse drug reactions in multiple subjects, the IMP should be administered to the second subject after the following day of Day 1 of Course 1 in the first subject at each dose level.
3) When the administration or examination scheduled for Course 1 cannot be implemented for reasons other than safety, the subject should be excluded from the DLT evaluation, and another subject should be enrolled.
4) Administration of SGI-110 is expected to cause myelosuppression and infection (eg, febrile neutropenia, pneumonia, and sepsis). Delay or discontinuation of administration should be determined for subjects who have experienced or are suspected to have experienced pyrexia or infection based on data from laboratory tests, physical examination (body temperature), and imaging tests before the start of the next course and continuing the treatment.
5) In and after Course 2 (extended treatment period), IMP administration may be suspended (skipped) from Day 2 and onwards at the discretion of the investigator or subinvestigator, depending on the subject's condition. Subjects who fall under any of the discontinuation criteria should be withdrawn from the trial.

4 Investigational Medicinal Products

4.1 Test Product and Comparator

4.1.1 Test Product

Code Name	SGI-110
Generic Name	Undecided
Chemical Name	Sodium (2R,3S,5R)-5-(4-amino-2-oxo-1,3,5-triazin-1 (2H)-yl)-2-(hydroxymethyl) tetrahydrofuran-3-yl ((2R,3S,5R)-5-(2-amino-6-oxo-1H-purin-9 (6H)-yl)-3-hydroxytetrahydrofuran-2-yl) methyl phosphate
Content and Formulation	SGI-110 for injection, 100 mg contains SGI-110 equivalent to 100 mg of free acid, as a lyophilized powder in a 5-mL glass vial. SGI-110 diluent

Code Name	SGI-110
	for reconstitution, 3 mL contains 3 mL of custom diluent for reconstitution in a 5-mL glass vial.
Storage Conditions	SGI-110 for injection, 100 mg: 2°C to 8°C SGI-110 diluent for reconstitution, 3 mL: 2°C to 30°C

4.1.2 Comparator

Not applicable

4.2 Packaging and Labeling

4.2.1 Packaging

Investigational medicinal products supplied will be SGI-110 for injection, 100 mg and SGI-110 diluent for reconstitution, 3 mL in 2 separate vials. Each vial is closed with a fluororesin laminated rubber stopper and a blue flip-off cap for SGI-110 for injection, 100 mg or a white flip-off cap for SGI-110 diluent for reconstitution, 3 mL.

4.2.2 Contents of Label

The information written on the label includes specification that the drug is for use in a clinical trial, the code name, lot number, expiration date, and storage conditions of the IMP, and the name and address of the sponsor.

5 Trial Population

5.1 Target Disease

AML

5.2 Inclusion Criteria

Patients meeting all of the following criteria at the time of screening will be included in this trial:

1) Male or female patients with a diagnosis of AML (World Health Organization [WHO] classification 2008).
   - Patients, 20 years of age or older, who are unresponsive to standard chemotherapy or have relapsed following standard chemotherapy
   - Patients, 65 years of age or older, who are not eligible for standard intensive chemotherapy and who meet at least one of the following criteria (applicable to Cohorts 1, 2, and 4 only):
     – AML from MDS, or secondary AML

- Chromosomal karyotype abnormality with poor prognosis [del (5q), del (7q), −5, −7, abnormality of 3q (q21;q26), t (6;9) (p23;q34), t (9;22) (q34;q11.2), abnormality of 11 (11q23), or complex karyotype of 3 or more unrelated abnormalities of any kind]
- Dysfunction of the heart (left ventricular ejection fraction [LVEF] < 50%) or lung (diffusing capacity of the lung for carbon monoxide [DLCO] or forced expiratory volume in the first second [FEV 1] < 50% of expected value) which is unrelated to AML
- ECOG PS of 2
- 75 years of age or older

2) Patients with ECOG PS of 0 to 2.
3) Patients with adequate vital organ function (patients whose clinical laboratory values meet the following conditions).
   a) Hepatic function: total bilirubin (T-Bil) ≤ 2 × upper limit of normal (ULN); AST and ALT ≤ 2.5 × ULN.
   b) Renal function: serum Cr ≤ 1.5 × ULN.
4) Female patients of childbearing potential must not be pregnant or breast feeding (pregnancy test will be performed at screening). Female patients of childbearing potential and all male patients must practice two medically acceptable methods of birth control and must not become pregnant or father a child while receiving treatment with SGI-110 and for 3 months following last dosing. If male patients have female partners of childbearing potential, those partners must also practice medically acceptable methods of birth control for the same period.
5) Patients who have undergone prior allogeneic hematopoietic stem cell transplantation must have no evidence of active graft-versus host disease (GVHD) and must be off immunosuppressive therapy by ≥ 2 weeks prior to the scheduled start of IMP administration.
6) Patients who have undergone no major surgery within 4 weeks prior to the scheduled start of IMP administration.
7) Patients who have undergone no chemotherapy within 2 weeks prior to the scheduled start of IMP administration, nor hematopoietic stem cell transplantation within 8 weeks prior to the scheduled start of IMP administration.
8) Patients who are able to provide written consent to participate in this trial by signing an informed consent form (ICF) that has been approved by an Institutional Review Board (IRB) (patients who are willing to comply with the protocol, including consent to hospitalization during Course 1).

[Rationale for inclusion criteria]

1) The target population of the trial will be patients with AML who are expected to respond to SGI-110 in reference to a preceding clinical trial conducted outside of Japan (Study SGI-110-01). It has been decided to select patients who do not respond

to conventional therapy or for whom generally accepted standard therapy are not available in accordance with the "Guidelines for Clinical Evaluation of Antimalignant Tumor Drugs." The lower limit of age is set as 20 years for patients who are unresponsive to standard therapy or have relapsed after treatment since informed consent can be obtained from subjects aged 20 years or older. The lower limit of age is set as 65 years for patients who are not eligible for standard intensive chemotherapy in reference to studies conducted outside of Japan.

As mentioned in Section 1.2.3 Trial Rationale, a regimen of SGI-110 at 60 mg/m^2 once daily for 10 days is planned to be adopted in Study SGI-110-06 in patients with relapsed or refractory AML. Therefore, the tolerability of SGI-110 at 60 mg/m^2 once daily for 10 days will be evaluated in patients with relapsed or refractory AML in Cohort 3 (60 mg/m^2 in 10-day regimen), which is consistent with the target population in Study SGI-110-06.

2), 3) These criteria have been provided to ensure the subjects' safety in reference to the "Guidelines for Clinical Evaluation of Antimalignant Tumor Drugs."

4) The criterion has been provided in consideration of the safety of fetuses and infants because SGI-110 has shown genotoxicity, teratogenicity, fetotoxicity, and embryotoxicity and it is unknown whether or not SGI-110 is transferred into breast milk.

5) to 7) The criteria have been provided to select patients having no effect of previous treatment in reference to the "Guidelines for Clinical Evaluation of Antimalignant Tumor Drugs" and a study conducted outside of Japan (Study SGI-110-01).

8) The criterion has been provided for ethical reasons based on Good Clinical Practice. Hospitalization during Course 1, which is the DLT evaluation period, is to be mandatory in reference to the "Guidelines for Clinical Evaluation of Antimalignant Tumor Drugs."

5.3 Exclusion Criteria

Patients falling under any of the following criteria at the time of screening will be excluded from this trial:

1) Patients with acute promyelocytic leukemia (APL) accompanied by t (15;17) (q22;q12) or (PML/RARA) karyotype abnormalities (including other variant types of APL).

2) Patients with multiple cancers (except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for at least 3 years).
3) Patients with life-threatening illnesses other than AML, such as uncontrolled medical conditions or organ system dysfunction which, in the opinion of the investigator or subinvestigator, could compromise the subject's safety or the study outcomes.
4) Patients with poorly controlled arrhythmias, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association (NYHA) Functional Classification.
5) Patients with symptomatic central nervous system involvement.
6) Patients who have received radiation therapy for extramedullary disease within 2 weeks prior to planned enrollment.
7) Patients with AEs (other than alopecia) of Grade 2 or higher from prior therapy for AML, at the time of screening for this trial.
8) Patients with febrile neutropenia.
9) Patients who are human immunodeficiency virus (HIV) antibody positive, hepatitis B virus (HBV)-DNA positive, or with active hepatitis C.
10) Patients who have taken any investigational drug or individually imported drug within 2 weeks prior to the scheduled start of IMP administration.
11) Patients who have been treated with systemic corticosteroids as treatment for their AML within 2 weeks prior to the scheduled start of IMP administration.
12) Patients with uncontrolled active systemic infections.
13) Patients who have hypersensitivity to decitabine, SGI-110, or IMP excipients.
14) Patients judged to be ineligible by the investigator or subinvestigator for any other reason.

[Rationale for exclusion criteria]

1) Patients with APL will be excluded because it is reported that the remission rate is high in patients treated with all-trans retinoic acid, arsenic trioxide, etc.

2), 5), 6), 10), 11) These criteria have been provided for reasons of subject safety and because the conditions mentioned in these criteria may affect efficacy evaluation.

3), 4), 7) to 9), 12), 13) These criteria have been provided for reasons of subject safety.

14) The criterion has been provided so that the investigator or subinvestigator can consider factors other than those mentioned above when selecting subjects.

Reference: NYHA Functional Classification

I	Presence of heart disease, but no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath), or anginal pain.
II	Slight limitation of physical activity. Comfortable at rest.

	Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath), or anginal pain.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Unable to carry on any physical activity without discomfort because of heart disease. Symptoms of heart failure or anginal pain at rest. If any physical activity is undertaken, discomfort increases.
(Additional)	IIs: Slight limitation of physical activity IIm: Moderate limitation of physical activity

Source: Guidelines for Diagnosis and Treatment of Cardiovascular Diseases (2004-2005 Joint Working Group report)
Guidelines for Treatment of Acute Heart Failure (2006 revision) - Digest Version
Societies participating in the Joint Working Group: Japanese Circulation Society, Japanese Association for Thoracic Surgery, Japanese Society for Cardiovascular Surgery, Japanese College of Cardiology, and Japanese Heart Failure Society
http://www.j-circ.or.jp/guideline/pdf/JCS2006_maruyama_d.pdf

6 Trial Design

6.1 Dose, Regimen, and Treatment Period

The total daily dose will be determined based on the subject's body surface area (BSA) calculated from height and weight prior to administration in each course, according to the treatment cohort.

SGI-110 will be administered SC at the determined daily dose after being reconstituted using the custom diluent provided.

In Cohorts 1, 2, and 4, subjects will receive SGI-110 once daily for 5 consecutive days (Day 1 to Day 5), followed by a 23-day non-dosing period (Day 6 to Day 28). One course will consist of 4 weeks (28 days). In Cohort 3, subjects will receive SGI-110 once daily for 10 days in total (SGI-110 will be administered for 5 consecutive days [Day 1 to Day 5], suspended for 2 days [Day 6 and Day 7], then administered for another 5 consecutive days [Day 8 to Day 12]), and the dosing will be suspended for 16 days (Day 13 to Day 28). One course will consist of 4 weeks (28 days).

The dose and regimen for each cohort is as follows:

Cohort 1 (36 mg/m^2, 5-day administration)

Cohort 2 (60 mg/m^2, 5-day administration)

Cohort 3 (60 mg/m^2, 10-day administration [ie, 5-day administration twice, with a non-dosing period in-between])

Cohort 4 (90 mg/m^2, 5-day administration)

SGI-110 for injection, 100 mg contains SGI-110 equivalent to 100 mg of free acid, as a lyophilized powder in a 5-mL glass vial. Subjects who complete IMP administration and all observations during the DLT evaluation period, and who do not have any apparent progression of AML, will be permitted to continue treatment with IMP following the DLT evaluation period if they wish, and will receive treatment according to the same dosing schedule as Course 1 (Cohorts 1, 2, and 4).

In Cohort 3, subjects will receive SGI-110 for 10 days in Course 1 (DLT evaluation period), for 10 or 5 days in Course 2 (Extended treatment period), for 5 days in Course 3 and subsequent courses. The investigator will determine whether or not the transition to Course 2 should be postponed and which regimen is used for each subject, as described below, based on the subject's condition (the percentage of blasts in the peripheral blood and bone marrow, and peripheral blood cell counts) at the completion of Course 1.

1) Has blasts in the peripheral blood: Subject will proceed to Course 2 without delay and receive SGI-110 for 10 days.
2) No blasts in the peripheral blood: The percentage of blasts in the bone marrow will be assessed.
    a) The percentage of blasts in the bone marrow is ≥5%: Subject will proceed to Course 2 without delay and receive SGI-110 for 10 days.
    b) The percentage of blasts in the bone marrow is <5%: The neutrophil and platelet counts in the peripheral blood will be assessed.
        i) The neutrophil count is ≥ 500/μL and platelet count is ≥ 50000/μL: Subject will proceed to Course 2 without delay and receive SGI-110 for 5 days.
        ii) The neutrophil count is < 500/μL or platelet count is < 50000/μL: Transition to Course 2 will be postponed, and the subject's peripheral blood will be assessed at least once a week. After that, if the subject has no blasts in the peripheral blood but the neutrophil and platelet counts are recovered to ≥ 500/μL and ≥ 50000/μL, respectively, he/she will proceed to Course 2 and receive SGI-110 for 5 days. If blasts are found in the subject's peripheral blood while his/her transition to Course 2 is on hold, he/she will proceed to Course 2 and receive SGI-110 for 10 days. For subjects whose transition to Course 2 is on hold because blasts are not found in his/her peripheral blood and the neutrophil and platelet counts are < 500/μL and < 50000/μL, respectively, it is possible to proceed to Course 2 and receive SGI-110 for either 5 or 10 days at the discretion of the investigator or subinvestigator based on the benefit-risk balance for the subject.

SGI-110 diluent for reconstitution, 3 mL contains 3 mL of custom diluent for reconstitution in a 5-mL glass vial.

SGI-110 for injection, 100 mg vial and SGI-110 diluent for reconstitution, 3 mL should be stored at 2°C to 8°C and 2°C to 30°C, respectively, until use. Both vials are for single use only as they are free of preservatives.

[Rationale for dose, regimen, and treatment period]

[Dose]

In the phase 1 part (ie, dose escalation segment) of a phase 1/2 trial conducted outside of Japan (Study SGI-110-01), no DLT occurred when SGI-110 was administered at a dose range of up to 90 mg/m^2 for 5 days to patients with MDS and patients with AML who had relapsed after standard therapy or had not responded to treatment, and 2 of 3 patients with MDS experienced DLTs (thrombocytopenia, neutropenia, febrile neutropenia, and sepsis) after administration at 125 mg/m^2. Hence, the MTD was estimated to be 90 mg/m^2 (no DLT occurred in patients with AML who had received SGI-110 at a dose range of up to 125 mg/m^2). The BED was determined to be 60mg/m^2 based on the evaluation of DNA hypomethylation in LINE-1. In the dose expansion segment implemented as the phase 2 part, two dose levels of 60 and 90mg/m^2 were compared in patients with AML who had relapsed after standard therapy or had not responded to treatment and treatment-naïve patients with AML who were not eligible for standard chemotherapy; the composite remission rates were very similar (25% and 26%, respectively).[11]

Based on these, the trial is designed to administer SGI-110 at an initial dose of 36 mg/m^2 (one level lower than 60 mg/m^2) for 5 days and then increase the dose to up to 90 mg/m^2 (one level higher than 60 mg/m^2) so as to evaluate the safety of 60 mg/m^2, the recommended dose for non-Japanese patients, in Japanese subjects.

[Regimen and treatment period]

In the dose escalation segment of Study SGI-110-01, 3 regimens were adopted for evaluation: ie, a 5-day regimen (Day 1 to Day 5), a once-weekly regimen (Day 1, Day 8, and Day 15), and a twice-weekly regimen (Day 1, Day 4, Day 8, Day 11, Day 15, and Day 18). At the end of the dose escalation segment, the Independent Data Monitoring Committee recommended transition to the dose expansion segment (ie, the phase 2 part) and adoption of a 5-day once-daily regimen in the dose expansion segment because the extent of hypomethylation was lower for the once-weekly regimen than for the 5-day once-daily regimen. Likewise, it was decided to adopt a 5-day once-daily regimen for the trial.

[Rationale for dose, regimen, and treatment period: Cohort 3]

A phase 1/2 trial was conducted outside of Japan (Study SGI-110-01) in patients with AML who had relapsed after standard chemotherapy or had not responded to treatment. Based on the results obtained in the dose expansion segment conducted as phase 2 segment in the Study SGI-110-01, which is shown below, 60 mg/m^2 once daily for 10 days has been chosen as a dose and treatment period for Cohort 3.

- When comparing 60 mg/m^2 in 5-day regimen with 90 mg/m^2 in 5-day regimen, there were no differences in remission rate and overall survival.
- When comparing 60 mg/m^2 in 5-day regimen with 60 mg/m^2 in 10-day regimen, the time to achieve complete remission was shorter and the extent of hypomethylation was more potent in 10-day regimen.

A phase 3 trial (Study SGI-110-06) in patients with relapsed or refractory AML is newly planned. Since the dose and treatment period of Study SGI-110-06 has been set as 60 mg/m^2 once daily for 10 days, the tolerability of the same regimen (60 mg/m^2 once daily for 10 days) in Japanese patients was decided to be evaluated in this study.

6.2 Prior and Concomitant Treatment

6.2.1 Prohibited Concomitant Drugs and Therapies

Only the IMP will be used for treating the primary disease, and concomitant use of the drugs and therapies listed below is prohibited from the time of informed consent to the withdrawal examination.

- Other anti-cancer drugs, hormone therapy, antibody therapy, radiation therapy, thermal therapy, or other anti-cancer therapies
- Other investigational drugs and individually imported drugs
- Prophylactic therapies for the purpose of preventing AEs (except infection) (Prophylactic therapies to prevent recurrence of AEs observed after the start of the IMP administration will be allowed.)

6.2.2 Restricted Concomitant Drugs and Therapies

Any drug or therapy that is not prohibited, as specified above, can be administered during the trial.

The investigator or subinvestigator should administer blood transfusions for supportive care as appropriate. Prophylactic medications should be provided if necessary in order to prevent bacterial, fungal, viral, and opportunistic infections and deaths from these

infections. Antibiotics and other drugs can be given to prevent and control febrile neutropenia. In the trial, febrile neutropenia is defined as a neutrophil count below 500/μL and body temperature of 38°C or higher.

Subjects with fever will undergo physical examination and peripheral blood tests (including differential leukocyte count and blood culture). Subjects who have been confirmed to have febrile neutropenia or sepsis (including suspected cases) by physical examination will be hospitalized and properly treated with a broad-spectrum antibiotic and other medication. The package insert should be observed for use of hematopoietic growth factors such as a granulocyte-colony stimulating factor.

When any drugs other than the IMP (excluding physiological saline and dextrose solution used for reconstitution) have been used from 28 days before the start of IMP administration until the date of withdrawal from the trial, the name of the drug, purpose of use, regimen, daily dose, route of administration, and start and end dates of treatment will be recorded in the case report form (CRF) (or in the medical records during the extended treatment part). If blood transfusion has been performed, the type, purpose, volume, and date of blood transfusion will be recorded in the CRF (or in the medical records during the extended treatment part). For treatments other than medication and blood transfusion, the name, purpose, and start and end dates of the therapy will be recorded in the CRF (or in the medical records during the extended treatment part).

[Rationales for prohibited concomitant drugs and therapies]

The prohibited concomitant drugs and therapies are specified because they may affect safety and efficacy evaluations. Supportive care used in routine medical practice, and medications to prevent infection, are allowed because patients in the trial are anticipated to have symptoms that may affect ADL such as decreased blood cell counts and infection associated with progression of the underlying disease, AML. In addition decreased blood cell counts are anticipated after IMP administration.

6.3 Method of Minimizing or Avoiding Bias

Not applicable

7 Trial Procedures

7.1 Schedule and Procedures

The investigator or subinvestigator will perform investigations, observations, examinations, and evaluations during the trial period in accordance with the "Schedule of Events" shown in Table 7.1-1. Items that trial associates are capable of performing, such as the patient background survey, may be performed by trial associates under the supervision of the investigator or subinvestigator.

Evaluation of DLTs, the primary objective of the trial, will take place from the first dosing in Course 1 to the examination scheduled for Day 29 of Course 1. However, the DLT evaluation period will last up until the first dosing in Course 2 for subjects who have postponed the start of IMP administration scheduled for Day 1 of Course 2 (extended treatment period).

The trial period for each subject will be from the day of informed consent to the day of withdrawal from the trial. However, if AEs (including abnormal changes in laboratory values) that occur during the trial period have not resolved by the date of withdrawal from the trial, they will be followed up in accordance with Section 8.4 Follow-up Investigation of Adverse Events.

Table 7.1-1 Schedule of Events

Cohorts 1, 2, and 4 (5-day Regimen)

			Primary Evaluation Part																			Extended Treatment Part		Withdrawal Examination[a]
			Course 1 (DLT Evaluation Period)[b]									Course 2 (Extended Treatment Period)						Course 3 and Subsequent Courses (Extended Treatment Period)				Extended Course		
	Screening		D1	D2	D3	D4	D5	D8	D15	D22	D29[c]	D1	D2-D5	D8	D15	D22	D29[c]	D1	D2-D5	D15	D29[c]	D1-D5	D29	Within 5 days after Withdrawal
Acceptable Time Window (Day)	**−28**	**−14**	**1**	**2**	**3**	**4**	**5**	**6-10**	**12-18**	**19-25**	**26-32**	**1**	**2-5**	**6-10**	**12-18**	**19-25**	**26-32**	**1**	**2-5**	**12-18**	**26-32**	**1-5**		
Written Consent[d]	○											○										○		
Patient Background Investigation	○																							
Investigation of Concomitant Drugs and Blood Transfusion[e]	←																				→	←		→	○
Investigation of AEs	←																				→	←		→	○
Medical Examination by Investigator or Subinvestigator (Subjective and Objective Findings)	○		○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Pregnancy Test (Urine or Serum Test)[f]		○									○													○
Viral Test[g]		○										○						○						
Verification of Eligibility, Enrollment		○																						
IMP Administration			↓	↓	↓	↓	↓					↓	↓					↓	↓			↓		
Vital Signs[h]		○	○	○	○	○	○	○	○	○	○	□	○	○	○	○	○	□	○	○	○			○
Height		○																						
Body Weight[i]			□								○	□						□						○
Twelve-lead ECG		○	□								○						○				○			○
Chest X-ray		○									○						○				○			○
Cardiac Function or Respiratory Function[j]		◊																						
Hematology Test[k]		○	□					○	○	○	○	□		○	○	○	○	□		○	○	□		○
Blood Biochemistry Test[l]		○	□								○	□					○	□			○			○

Table 7.1-1 Schedule of Events

Cohorts 1, 2, and 4 (5-day Regimen)

			Primary Evaluation Part																			Extended Treatment Part		Withdrawal Examination[a]
			Course 1 (DLT Evaluation Period)[b]									Course 2 (Extended Treatment Period)						Course 3 and Subsequent Courses (Extended Treatment Period)				Extended Course		
	Screening		D1	D2	D3	D4	D5	D8	D15	D22	D29[c]	D1	D2-D5	D8	D15	D22	D29[c]	D1	D2-D5	D15	D29[c]	D1-D5	D29	Within 5 days after Withdrawal
Acceptable Time Window (Day)	**−28**	**−14**	**1**	**2**	**3**	**4**	**5**	**6-10**	**12-18**	**19-25**	**26-32**	**1**	**2-5**	**6-10**	**12-18**	**19-25**	**26-32**	**1**	**2-5**	**12-18**	**26-32**	**1-5**		
Urinalysis[m]		○	□								○	□					○	□			○			○
ECOG PS		○									○						○				○			○
Bone Marrow Aspiration[n]		○									○	←·····→						←·····→						○
Blood Sampling for PK[o]			○	○	○	○	○																	
Blood Sampling for PD[p]			○					○	○	○	○													
Evaluation of Efficacy[q]											○						○				○			○

○: Mandatory item
□: If such tests or examinations have already been conducted within 4 days before Day 1, those tests/examinations may be used as the Day 1 tests/examinations.
◊: Optional item related to inclusion criteria

[a] If the withdrawal examination is performed within the acceptable time window for Day 8, Day 15, Day 22, or Day 29, repeated tests/examinations are not necessary for those items already performed for the same day. If the discontinuation is due to an SAE or progression of disease, only those examinations that are feasible, given the subject's state of health, will be performed.

[b] Hospitalization during Course 1 is mandatory. For those subjects for whom the trial is concluded with Course 1, hospitalization until the withdrawal examination is mandatory. For those subjects who continue to receive IMP administration in Course 2 and subsequent courses, hospitalization until commencement of IMP administration in Course 2 is mandatory.

[c] If IMP administration for the next course is started from Day 29, the tests designated for Day 29 should be performed between Day 26 and before IMP administration on Day 32. (If the tests designated for Day 29 are performed within the acceptable time window, between Day 26 and Day 28, IMP administration for the next course will be started on or after Day 29.)

[d] Written consent at screening will be obtained prior to all observations, tests, examinations, and evaluations of this trial. Written consent for continuation of IMP administration in Course 2 and subsequent courses will be obtained before the start of Course 2 (after Day 22 administration of Course 1).

[e] Details on all concomitant medications taken from 28 days before the start of IMP administration until discontinuation will be collected. Information on any blood transfusions administered from 28 days before the start of IMP administration until 30 days after the last administration will also be collected. (If the subject starts another AML treatment or is transferred to another hospital, collection of such data will be continued up until that point.)

[f] To be performed for female subjects only. (However, a pregnancy test is not required for subjects who have undergone bilateral oophorectomy or hysterectomy, or subjects who have been amenorrheic without a medical cause for at least 12 consecutive months.)

[g] Human immunodeficiency virus antibody, HBV-DNA, hepatitis C Virus (HCV) antibody, hepatitis B core antibody (HBcAB), and hepatitis B surface antibody (HBsAB) tests will be performed at screening. For those subjects who are found to be either HBcAB or HBsAB positive at screening, a test for HBV-DNA will be done on Day 1 in Course 2 and subsequent courses.

[h] Blood pressure (systolic/diastolic), pulse rate, body temperature (measured after the subject has rested in the sitting position for at least 3 minutes)

[i] Body weight will be measured and the dose of IMP to be administered will be determined according to the calculation of BSA.

[j] Cardiac function (echocardiography or multiple-gated acquisition [MUGA] scan) or respiratory function (DLCO or FEV 1) will be measured.

[k] Hemoglobin (Hb), hematocrit (Hct), RBC, WBC, differential WBC (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, promonocytes), platelet count, reticulocytes

[l] AST (glutamate oxaloacetate transaminase [GOT]), ALT (glutamate pyruvate transaminase [GPT]), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total protein (TP), albumin (ALB), T-Bil, blood urea nitrogen (BUN), uric acid (UA), Cr, blood glucose (fasting), Ca, Mg, Na, K, Cl

[m] Bilirubin, occult blood, protein, urobilinogen

[n] Bone marrow aspiration will be performed at screening and on Day 29 of Course 1. In Course 2 and subsequent courses, if peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed, bone marrow aspiration will be performed and the following items will be examined: percentage of bone marrow fluid (blasts, lymphoblasts, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, normoblasts, pronormoblasts, erythroblasts, plasma cells, and megakaryocytes), myeloid/erythroid ratio (M/E ratio), cellularity.
(If bone marrow aspiration has already been performed and any of the above items have been measured prior to acquisition of written informed consent and within the acceptable time window for the screening period [within 28 days before commencement of IMP administration], then those results can be used as the screening data, provided the subject's consent is obtained.)

[o] Blood sampling for PK:
Day 1 and Day 5: predose, 15 minutes, 30 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours after dosing
Day 2 (24 hours after Day 1 dosing), Day 3, and Day 4: predose (predose on Day 2 is the same as 24 hours postdose on Day 1)
[Acceptable time windows]

Day 1 and Day 5	predose:	Day 1: within 2 hours before IMP administration Day 5: ± 30 minutes of 24 hours from Day 4 dosing and before the Day 5 dosing
	15 minutes and 30 minutes postdose:	± 3 minutes
	60 minutes, 90 minutes, and 2 hours postdose:	± 6 minutes
	3 hours and 4 hours postdose:	± 12 minutes
	6 hours and 8 hours postdose:	± 24 minutes
	24 hours postdose:	± 30 minutes (24 hours postdose on Day 1 should be performed before Day 2 dosing)
Day 2, Day 3, Day 4	predose:	± 30 minutes of 24 hours from the previous dosing and before the dosing on that day

[p] Blood sampling for PD: blood sampling performed during screening is also acceptable for Day 1 sampling. If the sampling is performed on Day 1, it must be performed before dosing.

[q] In Course 2 and subsequent courses, evaluation of efficacy will be performed if peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed.

Table 7.1-1 Schedule of Events

Cohort 3 (10-day Regimen): 10-day Regimen in Course 2 (Extended Treatment Period)

			Primary Evaluation Part																							Extended Treatment Part		Withdrawal Examination[c]
			Course 1 (DLT Evaluation Period)[a]											Course 2 (Extended Treatment Period)[b]										Course 3 and Subsequent Courses (Extended Treatment Period)				Extended Course		
	Screening		D1	D2	D3	D4	D5	D8	D9-11	D12	D15	D22	D29[d]	D1	D2	D3	D4	D5	D8	D9-12	D15	D22	D29[d]	D1	D2-D5	D15	D29[d]	D1-5	D29	Within 5 days after Withdrawal
Acceptable Time Window (Day)	**−28**	**−14**	**1**	**2**	**3**	**4**	**5**	**8**	**9-11**	**12**	**13-18**	**19-25**	**26-32**	**1**	**2**	**3**	**4**	**5**	**8**	**9-12**	**13-18**	**19-25**	**26-32**	**1**	**2-5**	**12-18**	**26-32**	**1-5**		
Written Consent[e]	○													○														○		
Patient Background Investigation	○																													
Investigation of Concomitant Drugs and Blood Transfusion[f]	←																						→					←	→	○
Investigation of AEs	←																						→					←	→	○
Medical Examination by Investigator or Subinvestigator (Subjective and Objective Findings)	○		○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Pregnancy Test (Urine or Serum Test)[g]		○											○																	○
Viral Test[h]		○												○										○						
Verification of Eligibility, Enrollment		○																												
IMP Administration			↓	↓	↓	↓	↓	↓	↓	↓				↓	↓	↓	↓	↓	↓	↓				↓	↓			↓		
Vital Signs[i]		○	○	○	○	○	○	○	○	○	○	○	○	□	○	○	○	○	○	○	○	○	○	□	○	○	○			○
Height		○																												
Body Weight[j]			□										○	□										□						○
Twelve-lead ECG		○	□										○										○				○			○

Table 7.1-1 Schedule of Events

Cohort 3 (10-day Regimen): 10-day Regimen in Course 2 (Extended Treatment Period)

			Primary Evaluation Part																							Extended Treatment Part		Withdrawal Examination[c]
			Course 1 (DLT Evaluation Period)[a]											Course 2 (Extended Treatment Period)[b]										Course 3 and Subsequent Courses (Extended Treatment Period)				Extended Course		
	Screening		D1	D2	D3	D4	D5	D8	D9-11	D12	D15	D22	D29[d]	D1	D2	D3	D4	D5	D8	D9-12	D15	D22	D29[d]	D1	D2-D5	D15	D29[d]	D1-5	D29	Within 5 days after Withdrawal
Acceptable Time Window (Day)	−28	−14	1	2	3	4	5	8	9-11	12	13-18	19-25	26-32	1	2	3	4	5	8	9-12	13-18	19-25	26-32	1	2-5	12-18	26-32	1-5		
Chest X-ray		○											○										○				○			○
Cardiac Function or Respiratory Function[k]		◊																												
Hematology Test[l]		○	□					○			○	○	○	□					○		○	○	○	□		○	○	□		○
Blood Biochemistry Test[m]		○	□										○	□									○	□			○			○
Urinalysis[n]		○	□										○	□									○	□			○			○
ECOG PS		○											○										○				○			○
Bone Marrow Aspiration[o]		○											○	←									→	←			→			○
Blood Sampling for PK[p]			○	○			○			○																				
Blood Sampling for PD[q]			○					○			○	○	○																	
Evaluation of Efficacy[r]													○										○				○			○

Table 7.1-1 Schedule of Events

Cohort 3 (10-day Regimen): 5-day Regimen in Course 2 (Extended Treatment Period)

			Primary Evaluation Part																				Extended Treatment Part		Withdrawal Examination[c]
			Course 1 (DLT Evaluation Period)[a]											Course 2 (Extended Treatment Period)[b]						Course 3 and Subsequent Courses (Extended Treatment Period)				Extended Course		
	Screening		D1	D2	D3	D4	D5	D8	D9-11	D12	D15	D22	D29[d]	D1	D2-5	D8	D15	D22	D29[d]	D1	D2-D5	D15	D29[d]	D1-5	D29	Within 5 days after Withdrawal
Acceptable Time Window (Day)	−28	−14	1	2	3	4	5	8	9-11	12	13-18	19-25	26-32	1	2-5	6-10	12-18	19-25	26-32	1	2-5	12-18	26-32	1-5		
Written Consent[e]	○													○										○		
Patient Background Investigation	○																									
Investigation of Concomitant Drugs and Blood Transfusion[f]	←																							←	→	
Investigation of AEs	←																							←	→	
Medical Examination by Investigator or Subinvestigator (Subjective and Objective Findings)	○		○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Pregnancy Test (Urine or Serum Test)[g]		○											○													○
Viral Test[h]		○												○						○						
Verification of Eligibility, Enrollment		○																								
IMP Administration			↓	↓	↓	↓	↓	↓	↓	↓				↓	↓					↓	↓			↓		
Vital Signs[i]		○	○	○	○	○	○	○	○	○	○	○	○	□	○	○	○	○	○	□	○	○	○			○
Height		○																								
Body Weight[j]			□										○	□						□						○
Twelve-lead ECG		○	□										○						○				○			○
Chest X-ray		○											○						○				○			○
Cardiac Function or Respiratory Function[k]		◊																								

Table 7.1-1 Schedule of Events

Cohort 3 (10-day Regimen): 5-day Regimen in Course 2 (Extended Treatment Period)

			Primary Evaluation Part																				Extended Treatment Part		Withdrawal Examination[c]
			Course 1 (DLT Evaluation Period)[a]											Course 2 (Extended Treatment Period)[b]						Course 3 and Subsequent Courses (Extended Treatment Period)				Extended Course		
	Screening		D1	D2	D3	D4	D5	D8	D9-11	D12	D15	D22	D29[d]	D1	D2-5	D8	D15	D22	D29[d]	D1	D2-D5	D15	D29[d]	D1-5	D29	Within 5 days after Withdrawal
Acceptable Time Window (Day)	−28	−14	1	2	3	4	5	8	9-11	12	13-18	19-25	26-32	1	2-5	6-10	12-18	19-25	26-32	1	2-5	12-18	26-32	1-5		
Hematology Test[l]		○	□					○			○	○	○	□		○	○	○	○	□		○	○	□		○
Blood Biochemistry Test[m]		○	□										○	□					○	□			○			○
Urinalysis[n]		○	□										○	□					○	□			○			○
ECOG PS		○											○						○				○			○
Bone Marrow Aspiration[o]		○											○	←·····→						←·····→						○
Blood Sampling for PK[p]			○	○			○			○																
Blood Sampling for PD[q]			○					○			○	○	○													
Evaluation of Efficacy[r]													○						○				○			○

○: Mandatory item
□: If such tests or examinations have already been conducted within 4 days before Day 1, those tests/examinations may be used as the Day 1 tests/examinations.
◊: Optional item related to inclusion criteria

[a] Hospitalization during Course 1 is mandatory. For those subjects for whom the trial is concluded with Course 1, hospitalization until the withdrawal examination is mandatory. For those subjects who continue to receive IMP administration in Course 2 and subsequent courses, hospitalization until commencement of IMP administration in Course 2 is mandatory.

[b] Based on the subject's condition (the percentage of blasts in the peripheral blood and bone marrow, and peripheral blood cell counts) at the completion of Course 1, it will be determined whether or not the transition to Course 2 should be postponed and which regimen is used for each subject.

[c] If the withdrawal examination is performed within the acceptable time window for Day 15, Day 22, or Day 29, repeated tests/examinations are not necessary for those items already performed for the same day. If the discontinuation is due to a serious adverse event (SAE) or progression of disease, only those examinations that are feasible, given the subject's state of health, will be performed.

[d] If IMP administration for the next course is started from Day 29, the tests designated for Day 29 should be performed between Day 26 and before IMP administration on Day 32. (If the tests designated for Day 29 are performed within the acceptable time window, between Day 26 and Day 28, IMP administration for the next course will be started on or after Day 29.)

[e] Written consent at screening will be obtained prior to all observations, tests, examinations, and evaluations of this trial. Written consent for continuation of IMP administration in Course 2 and subsequent courses will be obtained before the start of Course 2 (after Day 22 administration of Course 1).

[f] Details on all concomitant medications taken from 28 days before the start of IMP administration until discontinuation will be collected. Information on any blood transfusions administered from 28 days before the start of IMP administration until 30 days after the last administration will also be collected. (If the subject starts another AML treatment or is transferred to another hospital, collection of such data will be continued up until that point.)

[g] To be performed for female subjects only. (However, a pregnancy test is not required for subjects who have undergone bilateral oophorectomy or hysterectomy, or subjects who have been amenorrheic without a medical cause for at least 12 consecutive months.)

[h] Human immunodeficiency virus antibody, HBV-DNA, hepatitis C virus (HCV) antibody, hepatitis B core antibody (HBcAB), and hepatitis B surface antibody (HBsAB) tests will be performed at screening. For those subjects who are found to be either HBcAB or HBsAB positive at screening, a test for HBV-DNA will be done on Day 1 in Course 2 and subsequent courses.

[i] Blood pressure (systolic/diastolic), pulse rate, body temperature (measured after the subject has rested in the sitting position for at least 3 minutes)

[j] Body weight will be measured and the dose of IMP to be administered will be determined according to the calculation of BSA.

[k] Cardiac function (echocardiography or multiple-gated acquisition [MUGA] scan) or respiratory function (DLCO or FEV 1) will be measured.

[l] Hemoglobin (Hb), hematocrit (Hct), red blood cell (RBC), white blood cell (WBC), differential WBC (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, promonocytes), platelet count, reticulocytes

[m] AST (glutamate oxaloacetate transaminase [GOT]), ALT (glutamate pyruvate transaminase [GPT]), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total protein (TP), albumin (ALB), T-Bil, blood urea nitrogen (BUN), uric acid (UA), Cr, blood glucose (fasting), Ca, Mg, Na, K, Cl

[n] Bilirubin, occult blood, protein, urobilinogen

[o] Bone marrow aspiration will be performed at screening and on Day 29 of Course 1. In Course 2 and subsequent courses, if peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed, bone marrow aspiration will be performed and the following items will be examined: percentage of bone marrow fluid (blasts, lymphoblasts, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, normoblasts, pronormoblasts, erythroblasts, plasma cells, and megakaryocytes), myeloid/erythroid ratio (M/E ratio), cellularity.
(If bone marrow aspiration has already been performed and any of the above items have been measured prior to acquisition of written informed consent and within the acceptable time window for the screening period [within 28 days before commencement of IMP administration], then those results can be used as the screening data, provided the subject's consent is obtained.)

[p] Blood sampling for PK:
Day 1 and Day 12: predose, 15 minutes, 30 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours after dosing
Day 5: 90 minutes, 6 hours after dosing
[Acceptable time windows]

Day 1 and Day 12	predose:	Day 1: within 2 hours before IMP administration Day 12: ± 30 minutes of 24 hours from Day 11 dosing and before the Day 12 dosing
	15 minutes and 30 minutes postdose:	± 3 minutes
	60 minutes, 90 minutes, and 2 hours postdose:	± 6 minutes
	3 hours and 4 hours postdose:	± 12 minutes

	6 hours and 8 hours postdose:	± 24 minutes
	24 hours postdose:	± 30 minutes (24 hours postdose on Day 1 should be performed before Day 2 dosing)
Day 5	90 minutes postdose:	± 6 minutes
	6 hours postdose:	± 24 minutes

[q] Blood sampling for PD: blood sampling performed during screening is also acceptable for Day 1 sampling. If the sampling is performed on Day 1, it must be performed before dosing.

[r] In Course 2 and subsequent courses, evaluation of efficacy will be performed if peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed.

7.1.1 Acquisition of Informed Consent

Prior to any medical procedures for the trial, including the screening examination, the investigator or subinvestigator will obtain written consent from subjects.

The investigator or subinvestigator will record the following subject information collected during the informed consent process in subject registration documents (list of screened subjects and list of enrolled subjects) and the CRF.

- Date of informed consent acquisition
- Subject number (3-digit trial site number + 4-digit in-site serial number)
- Subject identification code

Note For site numbers, see Annex 3, Lists of Trial Sites and Investigators Participating in the Trial.

7.1.2 Screening Examination

Examination items at screening are listed below. The investigator or subinvestigator will screen subjects who have provided consent based on data collected within 14 days before the start of treatment in Course 1. The use of data collected before informed consent will require the subject's consent for the use.

The following information collected from the screening examination and the date of examination and measurement will be documented in the medical records and CRF:

Examination items at screening[a]

Subject Background	Sex, date of birth, height, diagnosis of AML (WHO classification) and date of the diagnosis, prior treatment for AML (whether or not the subject has undergone hematopoietic stem cell transplantation [if yes, date of transplantation, type of transplantation, ie, bone marrow transplantation, peripheral blood stem cell transplantation, or cord blood transplantation; in case of bone marrow transplantation or peripheral blood stem cell transplantation, type of graft, ie, autograft or allograft] and response to the treatment; whether or not the subject has undergone radiation therapy [if yes, the start and end dates of therapy]; whether or not the subject has received other prior treatment for AML [if yes, type of treatment, the start and end dates of treatment, and regimen]) and response to the treatment, karyotype at screening, cytogenetic abnormalities, extramedullary lesions found after the diagnosis of AML and their sites, (maximum) proportion of blast cells (leukemia cells) in the bone marrow after the diagnosis of AML, diagnosis of malignancies other than AML, date of the diagnosis, treatment provided and date of healing, diagnosis of medically important past illness and date of the diagnosis, and diagnosis of complications found at the time of informed consent and date of the diagnosis
Clinical Symptoms	Subjective symptoms and objective findings
Pregnancy Test[b]	Urinary or serum HCG
Viral Test	HIV antibody, HBV-DNA, HCV antibody, HBcAB, and HBsAB

Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature
Twelve-lead ECG and Chest X-ray	Twelve-lead ECG and chest X-ray
Cardiac Function or Respiratory Function[c]	For cardiac function, LVEF will be measured by echocardiography or MUGA scan. For respiratory function, DLCO or FEV 1 will be measured.
Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes
Blood Biochemistry Test	AST (GOT), ALT (GPT), ALP, LDH, TP, ALB, T-Bil, BUN, UA, Cr, blood glucose (fasting), Ca, Mg, Na, K, and Cl
Urinalysis	Bilirubin, occult blood, protein, and urobilinogen
General Condition	ECOG PS
Bone Marrow Aspiration[d]	Percentage of bone marrow fluid (blasts, lymphoblasts, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, normoblasts, pronormoblasts, erythroblasts, plasma cells, and megakaryocytes), M/E ratio, and cellularity

HCG = Human chorionic gonadotropin

[a] For PD evaluation on Day 1, blood samples can be collected at the time of the screening examination.

[b] A pregnancy test will be performed in female subjects at the trial site. However, a pregnancy test is not required for subjects who have undergone bilateral oophorectomy or hysterectomy, or subjects who have been amenorrheic without a medical cause for at least 12 consecutive months.

[c] For cardiac function, LVEF will be measured by either echocardiography or MUGA scan according to the procedures specified by the trial site, and the date and results of measurement will be documented in the medical records and CRF. For respiratory function, DLCO or FEV 1 will be measured, and the date and results of measurement will be documented in the medical records and CRF.

[d] If bone marrow aspiration has already been performed and any of the above items have been measured prior to acquisition of written informed consent and within the acceptable time window for the screening period (within 28 days before commencement of IMP administration), then those results can be used as the screening data.

7.1.3 Subject Registration

The investigator or subinvestigator will record subjects who have provided consent, meet all the inclusion criteria, and do not fall under any of the exclusion criteria in a "registration request form," and send the form to the registration center. The registration center will send a "registration verification form" which provides the cohort number for the registered subject to the investigator or subinvestigator.

When an examination has been performed more than once during the screening period and on Day 1 of Course 1, the data closest to the registration date should be used to decide the eligibility.

7.1.4 Observations, Examinations, and Evaluations During the Treatment Period

7.1.4.1 Cohorts 1, 2, and 4 (5-day regimen)

7.1.4.1.1 Day 1 of Course 1

The observations, examinations, and evaluations listed below will be conducted before the start of IMP administration on Day 1 of Course 1, and the dates of the conduct and data obtained will be documented in the medical records and CRF. If measurement of body weight, 12-lead ECG, hematology test, blood biochemistry test, and urinalysis have been completed within 4 days before Day 1, the available data can be used instead.

If results of the examination conducted after registration or the subject's condition do not meet the inclusion criteria or fall under any of the exclusion criteria, IMP administration scheduled for Day 1 should not be started until the subject meets the inclusion criteria without falling under any of the exclusion criteria.

Clinical Symptoms	Subjective symptoms and objective findings
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature
Body Weight[a]	Body weight
Twelve-lead ECG	Twelve-lead ECG
Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes
Blood Biochemistry Test	AST (GOT), ALT (GPT), ALP, LDH, TP, ALB, T-Bil, BUN, UA, Cr, blood glucose (fasting), Ca, Mg, Na, K, and Cl
Urinalysis	Bilirubin, occult blood, protein, and urobilinogen

[a]Body weight will be measured and the dose of IMP to be administered will be determined according to the calculation of BSA.

For PK and PD evaluations, blood samples will be collected at the following timepoints:

PK Evaluation	Predose, and 15 minutes, 30 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, and 24 hours after dosing
PD Evaluation	Predose (blood can be collected at the time of the screening examination instead)

Hospitalization during Course 1 is mandatory. For those subjects for whom the trial is concluded with Course 1, hospitalization until the examination scheduled for Day 29 of Course 1 (until the withdrawal examination for those who are withdrawn from the trial in Course 1) is mandatory. For those subjects who continue to receive IMP administration in Course 2 and subsequent courses, hospitalization until commencement of IMP administration on Day 1 of Course 2 is mandatory.

7.1.4.1.2 Day 2 to Day 5 of Course 1

The observations, examinations, and evaluations listed below will be conducted before the start of IMP administration, and the dates of the conduct and data obtained will be documented in the medical records and CRF.

Clinical Symptoms	Subjective symptoms and objective findings
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature

For PK evaluation, blood samples will be collected at the following timepoints:

PK Evaluation	Day 2, Day 3, and Day 4: predose (predose blood sampling on Day 2 is the same as that at 24 hours postdose on Day 1) Day 5: predose, and 15 minutes, 30 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, and 24 hours after dosing

7.1.4.1.3 Day 8, Day 15, and Day 22 of Course 1

The observations, examinations, and evaluations listed below will be conducted, and the dates of the conduct and data obtained will be documented in the medical records and CRF.

Clinical Symptoms	Subjective symptoms and objective findings
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature
Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes
PD evaluation	Blood sampling

7.1.4.1.4 Day 29 of Course 1

The observations, examinations, and evaluations listed below will be conducted, and the dates of the conduct and data obtained will be documented in the medical records and CRF.

Clinical Symptoms	Subjective symptoms and objective findings
Pregnancy Test[a]	Urinary or serum HCG
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature
Body Weight	Body weight
Twelve-lead ECG and chest X-ray	Twelve-lead ECG and chest X-ray

Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes
Blood Biochemistry Test	AST (GOT), ALT (GPT), ALP, LDH, TP, ALB, T-Bil, BUN, UA, Cr, blood glucose (fasting), Ca, Mg, Na, K, and Cl
Urinalysis	Bilirubin, occult blood, protein, and urobilinogen
General Condition	ECOG PS
Bone Marrow Aspiration	Percentage of bone marrow fluid (blasts, lymphoblasts, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, normoblasts, pronormoblasts, erythroblasts, plasma cells, and megakaryocytes), M/E ratio, and cellularity
PD Evaluation	Blood sampling

HCG = Human chorionic gonadotropin

[a] A pregnancy test will be performed in female subjects at the trial site. However, a pregnancy test is not required for subjects who have undergone bilateral oophorectomy or hysterectomy, or subjects who have been amenorrheic without a medical cause for at least 12 consecutive months.

Prior to transition to Course 2 and subsequent courses, written informed consent (using written information for subjects) to extended treatment in Course 2 and subsequent courses will be obtained from subjects who wish to continue to receive the treatment and are eligible for extended treatment in the opinion of the investigator or subinvestigator (between Day 22 of Course 1 and the start of Course 2). In principle, each course should consist of 28 days, and if the examination scheduled for Day 29 is performed between Day 26 and Day 28 for example, which is within the acceptable window, IMP administration for the next course should be started on or after Day 29 of the current course.

7.1.4.1.5 Day 1 of Course 2

If written informed consent is obtained for extended treatment, the observations, examinations, and evaluations listed below will be conducted before the start of IMP administration on Day 1 of Course 2, and the dates of the conduct and data obtained will be documented in the medical records and CRF. If measurement of vital signs and body weight, hematology test, blood biochemistry test, and urinalysis have been completed within 4 days before Day 1, the available data can be used instead.

Clinical Symptoms	Subjective symptoms and objective findings
Viral Test[a]	HBV-DNA
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature
Body Weight[b]	Body weight

Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes
Blood Biochemistry Test	AST (GOT), ALT (GPT), ALP, LDH, TP, ALB, T-Bil, BUN, UA, Cr, blood glucose (fasting), Ca, Mg, Na, K, and Cl
Urinalysis	Bilirubin, occult blood, protein, and urobilinogen

If peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed, bone marrow aspiration will be performed.

[a] A viral test will be performed only in subjects who are found to be either HBcAB or HBsAB positive at screening.

[b] Body weight will be measured and the dose of IMP to be administered will be determined according to the calculation of BSA.

7.1.4.1.6 Day 2 to Day 5 of Course 2

The observations, examinations, and evaluations listed below will be conducted before the start of IMP administration, and the dates of the conduct and data obtained will be documented in the medical records and CRF.

Clinical Symptoms	Subjective symptoms and objective findings
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature

If peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed, bone marrow aspiration will be performed.

7.1.4.1.7 Day 8, Day 15, and Day 22 of Course 2

The observations, examinations, and evaluations listed below will be conducted, and the dates of the conduct and data obtained will be documented in the medical records and CRF.

Clinical Symptoms	Subjective symptoms and objective findings
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature
Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes

If peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed, bone marrow aspiration will be performed.

7.1.4.1.8 Day 29 of Course 2

The observations, examinations, and evaluations listed below will be conducted, and the dates of the conduct and data obtained will be documented in the medical records and CRF.

Clinical Symptoms	Subjective symptoms and objective findings
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature
Twelve-lead ECG and chest X-ray	Twelve-lead ECG and chest X-ray
Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes
Blood Biochemistry Test	AST (GOT), ALT (GPT), ALP, LDH, TP, ALB, T-Bil, BUN, UA, Cr, blood glucose (fasting), Ca, Mg, Na, K, and Cl
Urinalysis	Bilirubin, occult blood, protein, and urobilinogen
General Condition	ECOG PS

If peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed, bone marrow aspiration will be performed.

In principle, each course should consist of 28 days, and if the examination scheduled for Day 29 is performed between Day 26 and Day 28 for example, which is within the acceptable window, IMP administration for the next course should be started on or after Day 29 of the current course.

7.1.4.1.9 Day 1 of Course 3 and Subsequent Courses

The observations, examinations, and evaluations listed below will be conducted before the start of IMP administration on Day 1 of Course 3, and the dates of the conduct and data obtained will be documented in the medical records and CRF. If measurement of vital signs and body weight, hematology test, blood biochemistry test, and urinalysis have been completed within 4 days before Day 1, the available data can be used instead.

Clinical Symptoms	Subjective symptoms and objective findings
Viral Test[a]	HBV-DNA
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature
Body Weight[b]	Body weight
Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes
Blood Biochemistry Test	AST (GOT), ALT (GPT), ALP, LDH, TP, ALB, T-Bil, BUN, UA, Cr, blood glucose (fasting), Ca, Mg, Na, K, and Cl
Urinalysis	Bilirubin, occult blood, protein, and urobilinogen

If peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed, bone marrow aspiration will be performed.

[a] A viral test will be performed only in subjects who are found to be either HBcAB or HBsAB positive at screening.

[b] Body weight will be measured and the dose of IMP to be administered will be determined according to the calculation of BSA.

7.1.4.1.10 Day 2 to Day 5 of Course 3 and Subsequent Courses

The observations, examinations, and evaluations listed below will be conducted before the start of IMP administration, and the dates of the conduct and data obtained will be documented in the medical records and CRF.

Clinical Symptoms	Subjective symptoms and objective findings
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature

If peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed, bone marrow aspiration will be performed.

7.1.4.1.11 Day 15 of Course 3 and Subsequent Courses

The observations, examinations, and evaluations listed below will be conducted, and the dates of the conduct and data obtained will be documented in the medical records and CRF.

Clinical Symptoms	Subjective symptoms and objective findings
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature
Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes

If peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed, bone marrow aspiration will be performed.

7.1.4.1.12 Day 29 of Course 3 and Subsequent Courses

The observations, examinations, and evaluations listed below will be conducted, and the dates of the conduct and data obtained will be documented in the medical records and CRF.

Clinical Symptoms	Subjective symptoms and objective findings
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature
Twelve-lead ECG and chest X-ray	Twelve-lead ECG and chest X-ray
Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes
Blood Biochemistry Test	AST (GOT), ALT (GPT), ALP, LDH, TP, ALB, T-Bil, BUN, UA, Cr, blood glucose (fasting), Ca, Mg, Na, K, and Cl
Urinalysis	Bilirubin, occult blood, protein, and urobilinogen
General Condition	ECOG PS

If peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed, bone marrow aspiration will be performed.

In principle, each course should consist of 28 days, and if the examination scheduled for Day 29 is performed between Day 26 and Day 28 for example, which is within the acceptable window, IMP administration for the next course should be started on or after Day 29 of the current course. Written informed consent (using written information for subjects) will be obtained from subjects who wish to continue to receive the treatment in the extended treatment part and are eligible for extended treatment in the opinion of the investigator or subinvestigator (before the start of a new course in the extended treatment part).

7.1.4.1.13 Day 1 to Day 29 of the Extended Course in the Extended Treatment Part

The observations, examinations, and evaluations listed below will be conducted before the start of IMP administration on Day 1 of each course and during each course, and the dates of the conduct and data obtained will be documented in the medical records. In addition, examinations related to safety will be performed as necessary, and the dates of the conduct and data obtained will be documented in the medical records.

Clinical Symptoms	Subjective symptoms and objective findings
Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes

7.1.4.2 Cohort 3 (10-day regimen)

7.1.4.2.1 Day 1 of Course 1

The observations, examinations, and evaluations listed below will be conducted before the start of IMP administration on Day 1 of Course 1, and the dates of the conduct and data obtained will be documented in the medical records and CRF. If measurement of body weight, 12-lead ECG, hematology test, blood biochemistry test, and urinalysis have been completed within 4 days before Day 1, the available data can be used instead.

If results of the examination conducted after registration or the subject's condition do not meet the inclusion criteria or fall under any of the exclusion criteria, IMP administration scheduled for Day 1 should not be started until the subject meets the inclusion criteria without falling under any of the exclusion criteria.

Clinical Symptoms	Subjective symptoms and objective findings
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature
Body Weight[a]	Body weight
Twelve-lead ECG	Twelve-lead ECG

Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes
Blood Biochemistry Test	AST (GOT), ALT (GPT), ALP, LDH, TP, ALB, T-Bil, BUN, UA, Cr, blood glucose (fasting), Ca, Mg, Na, K, and Cl
Urinalysis	Bilirubin, occult blood, protein, and urobilinogen

[a]Body weight will be measured and the dose of IMP to be administered will be determined according to the calculation of BSA.

For PK and PD evaluations, blood samples will be collected at the following timepoints:

PK Evaluation	Predose, and 15 minutes, 30 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, and 24 hours after dosing
PD Evaluation	Predose (blood can be collected at the time of the screening examination instead)

Hospitalization during Course 1 is mandatory. For those subjects for whom the trial is concluded with Course 1, hospitalization until the examination scheduled for Day 29 of Course 1 (until the withdrawal examination for those who are withdrawn from the trial in Course 1) is mandatory. For those subjects who continue to receive IMP administration in Course 2 and subsequent courses, hospitalization until commencement of IMP administration on Day 1 of Course 2 is mandatory.

7.1.4.2.2 Day 2 to Day 5 and Day 9 to Day 12 of Course 1

The observations, examinations, and evaluations listed below will be conducted before the start of IMP administration, and the dates of the conduct and data obtained will be documented in the medical records and CRF.

Clinical Symptoms	Subjective symptoms and objective findings
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature

For PK and PD evaluation, blood samples will be collected at the following timepoints:

PK Evaluation	Day 2: predose (predose blood sampling on Day 2 is the same as that at 24 hours postdose on Day 1) Day 5: 90 minutes and 6 hours after dosing Day 12: predose, and 15 minutes, 30 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, and 24 hours after dosing
PD Evaluation	Day 8: predose

7.1.4.2.3 Day 8, Day 15, and Day 22 of Course 1

The observations, examinations, and evaluations listed below will be conducted, and the dates of the conduct and data obtained will be documented in the medical records and CRF.

Clinical Symptoms	Subjective symptoms and objective findings
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature
Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes
PD evaluation	Blood sampling

7.1.4.2.4 Day 29 of Course 1

The observations, examinations, and evaluations listed below will be conducted, and the dates of the conduct and data obtained will be documented in the medical records and CRF.

Clinical Symptoms	Subjective symptoms and objective findings
Pregnancy Test[a]	Urinary or serum HCG
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature
Body Weight	Body weight
Twelve-lead ECG and chest X-ray	Twelve-lead ECG and chest X-ray
Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes
Blood Biochemistry Test	AST (GOT), ALT (GPT), ALP, LDH, TP, ALB, T-Bil, BUN, UA, Cr, blood glucose (fasting), Ca, Mg, Na, K, and Cl
Urinalysis	Bilirubin, occult blood, protein, and urobilinogen
General Condition	ECOG PS
Bone Marrow Aspiration	Percentage of bone marrow fluid (blasts, lymphoblasts, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, normoblasts, pronormoblasts, erythroblasts, plasma cells, and megakaryocytes), M/E ratio, and cellularity
PD Evaluation	Blood sampling

HCG = Human chorionic gonadotropin

[a] A pregnancy test will be performed in female subjects at the trial site. However, a pregnancy test is not required for subjects who have undergone bilateral oophorectomy or hysterectomy, or subjects who have been amenorrheic without a medical cause for at least 12 consecutive months.

Prior to transition to Course 2, it will be assessed when to start Course 2 and which regimen (10-day regimen or 5-day regimen) to use in reference to Section 6.1 Dose, Regimen, and Treatment Period.

Written informed consent (using written information for subjects) to extended treatment in Course 2 and subsequent courses will be obtained from subjects who wish to continue to receive the treatment and are eligible for extended treatment in the opinion of the investigator or subinvestigator (between Day 22 of Course 1 and the start of Course 2). In principle, each course should consist of 28 days, and if the examination scheduled for Day 29 is performed between Day 26 and Day 28 for example, which is within the acceptable window, IMP administration for the next course should be started on or after Day 29 of the current course.

7.1.4.2.5 Day 1 of Course 2 (10-day regimen)

If written informed consent is obtained for extended treatment, the observations, examinations, and evaluations listed below will be conducted before the start of IMP administration on Day 1 of Course 2, and the dates of the conduct and data obtained will be documented in the medical records and CRF. If measurement of vital signs and body weight, hematology test, blood biochemistry test, and urinalysis have been completed within 4 days before Day 1, the available data can be used instead.

Clinical Symptoms	Subjective symptoms and objective findings
Viral Test[a]	HBV-DNA
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature
Body Weight[b]	Body weight
Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes
Blood Biochemistry Test	AST (GOT), ALT (GPT), ALP, LDH, TP, ALB, T-Bil, BUN, UA, Cr, blood glucose (fasting), Ca, Mg, Na, K, and Cl
Urinalysis	Bilirubin, occult blood, protein, and urobilinogen

If peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed, bone marrow aspiration will be performed.

[a] A viral test will be performed only in subjects who are found to be either HBcAB or HBsAB positive at screening.

[b] Body weight will be measured and the dose of IMP to be administered will be determined according to the calculation of BSA.

7.1.4.2.6 Day 2 to Day 5 and Day 9 to Day 12 of Course 2 (10-day regimen)

The observations, examinations, and evaluations listed below will be conducted before the start of IMP administration, and the dates of the conduct and data obtained will be documented in the medical records and CRF.

Clinical Symptoms	Subjective symptoms and objective findings
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature

If peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed, bone marrow aspiration will be performed.

7.1.4.2.7 Day 8, Day 15, and Day 22 of Course 2 (10-day regimen)

The observations, examinations, and evaluations listed below will be conducted, and the dates of the conduct and data obtained will be documented in the medical records and CRF.

Clinical Symptoms	Subjective symptoms and objective findings
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature
Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes

If peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed, bone marrow aspiration will be performed.

7.1.4.2.8 Day 29 of Course 2 (10-day regimen)

The observations, examinations, and evaluations listed below will be conducted, and the dates of the conduct and data obtained will be documented in the medical records and CRF.

Clinical Symptoms	Subjective symptoms and objective findings
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature
Twelve-lead ECG and chest X-ray	Twelve-lead ECG and chest X-ray
Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes
Blood Biochemistry Test	AST (GOT), ALT (GPT), ALP, LDH, TP, ALB, T-Bil, BUN, UA, Cr, blood glucose (fasting), Ca, Mg, Na, K, and Cl
Urinalysis	Bilirubin, occult blood, protein, and urobilinogen
General Condition	ECOG PS

If peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed, bone marrow aspiration will be performed.

In principle, each course should consist of 28 days, and if the examination scheduled for Day 29 is performed between Day 26 and Day 28 for example, which is within the acceptable window, IMP administration for the next course should be started on or after Day 29 of the current course.

7.1.4.2.9 Day 1 of Course 2 (5-day regimen)

If written informed consent is obtained for extended treatment, the observations, examinations, and evaluations listed below will be conducted before the start of IMP administration on Day 1 of Course 2, and the dates of the conduct and data obtained will be documented in the medical records and CRF. If measurement of vital signs and body weight, hematology test, blood biochemistry test, and urinalysis have been completed within 4 days before Day 1, the available data can be used instead.

Clinical Symptoms	Subjective symptoms and objective findings
Viral Test[a]	HBV-DNA
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature
Body Weight[b]	Body weight
Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes
Blood Biochemistry Test	AST (GOT), ALT (GPT), ALP, LDH, TP, ALB, T-Bil, BUN, UA, Cr, blood glucose (fasting), Ca, Mg, Na, K, and Cl
Urinalysis	Bilirubin, occult blood, protein, and urobilinogen

If peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed, bone marrow aspiration will be performed.

[a] A viral test will be performed only in subjects who are found to be either HBcAB or HBsAB positive at screening.

[b] Body weight will be measured and the dose of IMP to be administered will be determined according to the calculation of BSA.

7.1.4.2.10 Day 2 to Day 5 of Course 2 (5-day regimen)

The observations, examinations, and evaluations listed below will be conducted before the start of IMP administration, and the dates of the conduct and data obtained will be documented in the medical records and CRF.

Clinical Symptoms	Subjective symptoms and objective findings
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature

If peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed, bone marrow aspiration will be performed.

7.1.4.2.11 Day 8, Day 15, and Day 22 of Course 2 (5-day regimen)

The observations, examinations, and evaluations listed below will be conducted, and the dates of the conduct and data obtained will be documented in the medical records and CRF.

Clinical Symptoms	Subjective symptoms and objective findings
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature
Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes

If peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed, bone marrow aspiration will be performed.

7.1.4.2.12 Day 29 of Course 2 (5-day regimen)

The observations, examinations, and evaluations listed below will be conducted, and the dates of the conduct and data obtained will be documented in the medical records and CRF.

Clinical Symptoms	Subjective symptoms and objective findings
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature
Twelve-lead ECG and chest X-ray	Twelve-lead ECG and chest X-ray
Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes
Blood Biochemistry Test	AST (GOT), ALT (GPT), ALP, LDH, TP, ALB, T-Bil, BUN, UA, Cr, blood glucose (fasting), Ca, Mg, Na, K, and Cl
Urinalysis	Bilirubin, occult blood, protein, and urobilinogen
General Condition	ECOG PS

If peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed, bone marrow aspiration will be performed.

In principle, each course should consist of 28 days, and if the examination scheduled for Day 29 is performed between Day 26 and Day 28 for example, which is within the acceptable window, IMP administration for the next course should be started on or after Day 29 of the current course.

7.1.4.2.13 Day 1 of Course 3 and Subsequent Courses (5-day regimen)

The observations, examinations, and evaluations listed below will be conducted before the start of IMP administration on Day 1 of Course 3, and the dates of the conduct and data obtained will be documented in the medical records and CRF. If measurement of

vital signs and body weight, hematology test, blood biochemistry test, and urinalysis have been completed within 4 days before Day 1, the available data can be used instead.

Clinical Symptoms	Subjective symptoms and objective findings
Viral Test[a]	HBV-DNA
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature
Body Weight[b]	Body weight
Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes
Blood Biochemistry Test	AST (GOT), ALT (GPT), ALP, LDH, TP, ALB, T-Bil, BUN, UA, Cr, blood glucose (fasting), Ca, Mg, Na, K, and Cl
Urinalysis	Bilirubin, occult blood, protein, and urobilinogen

If peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed, bone marrow aspiration will be performed.

[a] A viral test will be performed only in subjects who are found to be either HBcAB or HBsAB positive at screening.

[b] Body weight will be measured and the dose of IMP to be administered will be determined according to the calculation of BSA.

7.1.4.2.14 Day 2 to Day 5 of Course 3 and Subsequent Courses (5-day regimen)

The observations, examinations, and evaluations listed below will be conducted before the start of IMP administration, and the dates of the conduct and data obtained will be documented in the medical records and CRF.

Clinical Symptoms	Subjective symptoms and objective findings
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature

If peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed, bone marrow aspiration will be performed.

7.1.4.2.15 Day 15 of Course 3 and Subsequent Courses (5-day regimen)

The observations, examinations, and evaluations listed below will be conducted, and the dates of the conduct and data obtained will be documented in the medical records and CRF.

Clinical Symptoms	Subjective symptoms and objective findings
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature
Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes

If peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed, bone marrow aspiration will be performed.

7.1.4.2.16 Day 29 of Course 3 and Subsequent Courses (5-day regimen)

The observations, examinations, and evaluations listed below will be conducted, and the dates of the conduct and data obtained will be documented in the medical records and CRF.

Clinical Symptoms	Subjective symptoms and objective findings
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature
Twelve-lead ECG and chest X-ray	Twelve-lead ECG and chest X-ray
Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes
Blood Biochemistry Test	AST (GOT), ALT (GPT), ALP, LDH, TP, ALB, T-Bil, BUN, UA, Cr, blood glucose (fasting), Ca, Mg, Na, K, and Cl
Urinalysis	Bilirubin, occult blood, protein, and urobilinogen
General Condition	ECOG PS

If peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed, bone marrow aspiration will be performed.

In principle, each course should consist of 28 days, and if the examination scheduled for Day 29 is performed between Day 26 and Day 28 for example, which is within the acceptable window, IMP administration for the next course should be started on or after Day 29 of the current course.

7.1.4.2.17 Day 1 to Day 29 of the Extended Course in the Extended Treatment Part

The observations, examinations, and evaluations listed below will be conducted before the start of IMP administration on Day 1 of each course and during each course, and the dates of the conduct and data obtained will be documented in the medical records. In addition, examinations related to safety will be performed as necessary, and the dates of the conduct and data obtained will be documented in the medical records.

Clinical Symptoms	Subjective symptoms and objective findings
Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes

7.1.5 Observations, Examinations, and Evaluations at the Time of Withdrawal

The observations, examinations, and evaluations listed below will be conducted within 5 days after withdrawal from the trial has been decided, and the dates of the conduct and

data obtained will be documented in the medical records and CRF. If the withdrawal examination takes place within the acceptable time window for Day 8, Day 15, Day 22, or Day 29, it is not necessary to repeat items that have been performed in the examinations for Day 8, Day 15, Day 22, or Day 29 for the withdrawal examination. If the withdrawal is due to an SAE or progression of the primary disease, only those examinations that are feasible, given the subject's state of health, will be performed in consideration of the subject's conditions.

Clinical Symptoms	Subjective symptoms and objective findings
Pregnancy Test[a]	Urinary or serum HCG
Vital Signs	Blood pressure (systolic/diastolic), pulse rate, and body temperature
Body Weight	Body weight
Twelve-lead ECG and chest X-ray	Twelve-lead ECG and chest X-ray
Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes
Blood Biochemistry Test	AST (GOT), ALT (GPT), ALP, LDH, TP, ALB, T-Bil, BUN, UA, Cr, blood glucose (fasting), Ca, Mg, Na, K, and Cl
Urinalysis	Bilirubin, occult blood, protein, and urobilinogen
General Condition	ECOG PS
Bone Marrow Aspiration[b]	Percentage of bone marrow fluid (blasts, lymphoblasts, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, normoblasts, pronormoblasts, erythroblasts, plasma cells, and megakaryocytes), M/E ratio, and cellularity

HCG = Human chorionic gonadotropin

[a] A pregnancy test will be performed in female subjects at the trial site. However, a pregnancy test is not required for subjects who have undergone bilateral oophorectomy or hysterectomy, or subjects who have been amenorrheic without a medical cause for at least 12 consecutive months.

[b] If peripheral blood testing indicates that the subject meets criteria for remission, or if clear disease progression is observed, bone marrow aspiration will be performed.

7.2 Method of Evaluation

7.2.1 Safety Evaluation (Primary Evaluation Part)

7.2.1.1 Clinical Symptoms

The investigator or subinvestigator will examine subjects at the timepoints stipulated in the protocol, and record subjective symptoms and objective findings that are deemed to be AEs in the CRF.

7.2.1.2 Dose Limiting-toxicities and Adverse Events

Dose limiting-toxicities and AEs will be assessed in accordance with the CTCAE version 4.0. See the sections on AEs for details.

Occurrence of DLTs will be recorded in the CRF in a timely manner after the end of the DLT evaluation period, and if any DLT occurs, detailed information of the DLT (date of onset, severity, seriousness, outcome, and relationship with the IMP) as well as the status of IMP administration in Course 1 will be also recorded in the CRF. In Course 2 and subsequent courses as well, detailed information of any DLTs will be recorded in the CRF.

7.2.1.3 Body Weight

Body weight will be measured in accordance with the procedures specified at the trial site, and the date of measurement and data obtained will be documented in the medical records and CRF.

7.2.1.4 General Condition

Each subject's general condition will be assessed by reference to the Japanese version of the ECOG PS, and the date of assessment and assessment results will be documented in the medical records and CRF. Death will be scored as 5.

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, e.g., light house work, 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.

These criteria are indices for general condition. Activity restricted because of local symptoms should be based on clinical judgment.

Source: Common Toxicity Criteria Version 2.0 published on 30 April 1999 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf); website of Japan Clinical Oncology Group (http://www.jcog.jp/)

7.2.1.5 Vital Signs (Blood Pressure, Pulse Rate, and Body Temperature)

Blood pressure (systolic/diastolic), pulse rate, and body temperature will be measured (in the sitting position after 3-minute rest), and the date of measurement and data obtained will be documented in the medical records and CRF.

7.2.1.6 Twelve-lead Electrocardiogram

Twelve-lead ECG will be performed in accordance with the procedures specified at the trial site. A central ECG reading facility will analyze heart rate, PR interval, RR interval,

QRS interval, QT interval, and corrected QT interval (QTc interval). The QT interval (QT interval as corrected by Fridericia's formula [QTcF interval]) will be calculated using the following formula: $QTcF = (QT\ interval/RR\ interval)^{1/3}$. The central ECG reading facility will report analysis results to the investigator or subinvestigator. Then, the investigator or subinvestigator will check the results, and sign the analysis report and enter the date of confirmation. The investigator or subinvestigator will decide whether the ECG is normal or abnormal based on the analysis results submitted by the central ECG reading facility, and will document the decision and the date and time of the examination in the medical records and CRF. Clinically significant findings will be assessed as AEs.

7.2.1.7 Chest X-ray

A chest X-ray will be taken in accordance with the procedures specified at the trial site, and the date of examination and findings obtained will be documented in the medical records and CRF. Clinically significant findings will be assessed as AEs.

7.2.1.8 Hematology Test, Blood Biochemistry Test, and Urinalysis

Blood and urine samples will be collected for determination of the parameters listed below in accordance with the procedures specified by the trial site. The dates of blood sampling and urine collection, and measurement results will be documented in the medical records and CRF.

Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes
Blood Biochemistry Test	AST (GOT), ALT (GPT), ALP, LDH, TP, ALB, T-Bil, BUN, UA, Cr, blood glucose (fasting), Ca, Mg, Na, K, and Cl
Urinalysis	Bilirubin, occult blood, protein, and urobilinogen

7.2.2 Safety Evaluation (Extended Treatment Part)

7.2.2.1 Clinical Symptoms

The investigator or subinvestigator will examine subjects at the timepoints stipulated in the protocol, and document subjective symptoms and objective findings that are deemed to be AEs in the medical records.

7.2.2.2 Adverse Events

Adverse events will be assessed in accordance with the CTCAE version 4.0, and their details will be documented in the medical records. See the sections on AEs for details.

7.2.2.3 Hematology Test

Blood samples will be collected for determination of the parameters listed below in accordance with the procedures specified by the trial site. The date of blood sampling and measurement results will be documented in the medical records.

Hematology Test	Hb, Hct, RBC count, WBC count, differential WBC count (visual count: blast cells [leukemia cells], lymphoblastoid cells, monoblasts, promyelocytes, myelocytes, metamyelocytes, segmented neutrophils, stab leucocytes, lymphocytes, eosinophils, monocytes, basophils, prolymphocytes, and promonocytes), platelet count, and reticulocytes

7.2.3 Efficacy Evaluation

7.2.3.1 Assessment Based on Response Criteria

The investigator or subinvestigator will evaluate response in each course in accordance with the response criteria in Table 7.2-1, which is based on the response criteria for AML treatment established by an international working group,[10] and will document evaluation results in the medical records and CRF. The evaluation results to be documented in the medical records and CRF will be "not evaluable (NE)" when no bone marrow examination has been performed, "progressive disease" when disease clearly progressed without CR, CRi, or CRp achieved after the start of IMP administration, or "no response" when no remission or relapse has been confirmed in the course.

The best overall response for each subject and the date of the first response (CR, CRi, or CRp) will be documented in the medical records and CRF at the time of trial completion or withdrawal from the trial. Also recorded will be the date of the first relapse, if relapse occurred thereafter, and the date of the last evaluation, if no relapse occurred.

Table 7.2-1 Response Criteria

	Bone Marrow	Peripheral Blood
CR	• Blast cells < 5%	• Neutrophil count > 1,000/μL • Platelet count ≥ 100,000/μL • No blast cell • Transfusion independence
CRp	• Blast cells < 5%	• Neutrophil count > 1,000/μL • Platelet count < 100,000/μL • No blast cell • RBC transfusion independence
Morphologic CRi	• Blast cells < 5 %	• Neutrophil count < 1,000/μL • No blast cell
PR	• Rate of decrease in blast cells in the bone marrow ≥ 50% and ratio of blast cells of 5% to 25%	• Neutrophil count > 1,000/μL • Platelet count ≥ 100,000/μL • No blast cell
Relapse	• Leukemia cells (blast cells) ≥ 5% in the bone marrow or presence of leukemia cells (blast cells) in the peripheral blood are manifested again after CR, CRi, or CRp has been achieved. • Leukemia cells with abnormal chromosomes are revealed again in chromosomal testing.	

7.2.3.2 Outcome of Survival

The survival of each subject will be investigated at the end of the primary evaluation part of the trial (see Section 15 Scheduled Duration of the Trial) and recorded in the CRF. The date of survival confirmation will be recorded in the CRF if the subject is alive, the date of death and its reason if the subject has died, and the date of final survival confirmation if it is unknown whether the subject is alive.

7.2.3.3 Investigations of Acute Myeloid Leukemia Treatments after Trial Discontinuation

Treatment for AML given on or after the date of withdrawal from the trial will be investigated from the date of withdrawal from the trial until the end of the primary evaluation part in the trial (see Section 15 Scheduled Duration of the Trial), and detailed information and the start date of the subsequent AML treatment will be documented in the medical records and CRF.

7.2.4 Pharmacokinetic Evaluation

Blood will be sampled and processed in accordance with the following procedures, and the plasma samples will be cryopreserved at ≤ −70°C (preset temperature) until collection

by the sample collecting facility. The sample collecting facility will transport the samples packed in dry ice to the laboratory performing drug concentration measurements.

1) Blood sampling
At each blood sampling timepoint, 6 mL of blood will be drawn into a tube containing tetrahydrouridine and di-potassium ethylenediaminetetraacetic acid (EDTA). The tube will be slowly inverted 8 to 10 times to mix the blood with these agents and kept in an ice bath until centrifugation. The sample tubes will be centrifuged within 2 hours after sampling at 1800 g and approximately 4°C for 10 minutes or at 1500 g and approximately 4°C for 15 minutes. The separated plasma will be transferred into two labelled polypropylene tubes (primary sample and backup sample). The date and time of blood sampling will be documented in the medical records and CRF.

2) Blood sampling timepoints
[Cohorts 1, 2, and 4]
Day 1 and Day 5: predose, 15 minutes, 30 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, and 24 hours (Day 5) after dosing
Day 2, Day 3, and Day 4: predose (predose on Day 2 is the same as 24 hours postdose on Day 1.)

[Acceptable time windows]

Day 1 and Day 5	Predose on Day 1: within 2 hours before IMP administration Predose on Day 5: ± 30 minutes of 24 hours from Day 4 dosing and before the Day 5 dosing 15 minutes and 30 minutes postdose: ± 3 minutes 60 minutes, 90 minutes, and 2 hours postdose: ± 6 minutes 3 hours and 4 hours postdose: ± 12 minutes 6 hours and 8 hours postdose: ± 24 minutes 24 hours postdose: ± 30 minutes (24 hours postdose on Day 1 should be performed before Day 2 dosing)
Day 2, Day 3, and Day 4	Predose: ± 30 minutes of 24 hours from the previous dosing and before the dosing on that day

[Cohort 3]
Day 1 and Day 12: predose, 15 minutes, 30 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, and 24 hours after dosing
Day 5: 90 minutes and 6 hours after dosing

[Acceptable time windows]

Day 1 and Day 12	Predose on Day 1: within 2 hours before IMP administration Predose on Day 12: ± 30 minutes of 24 hours from Day 11 dosing and before the Day 12 dosing 15 minutes and 30 minutes postdose: ± 3 minutes 60 minutes, 90 minutes, and 2 hours postdose: ± 6 minutes 3 hours and 4 hours postdose: ± 12 minutes 6 hours and 8 hours postdose: ± 24 minutes 24 hours postdose: ± 30 minutes (24 hours postdose on Day 1 should be performed before Day 2 dosing)

Day 5	90 minutes postdose: ± 6 minutes 6 hours postdose: ± 24 minutes

3) Plasma drug concentration measurement
Plasma concentrations (of SGI-110 and its active metabolite [decitabine]) will be measured using the liquid chromatography-tandem mass spectrometry method validated by Frontage Laboratories Inc. Remaining samples after the plasma drug concentration measurement will be stored at Frontage Laboratories Inc. until after the CSR is prepared and the sponsor instructs them to be discarded.
Measurement results will be reported electronically by Frontage Laboratories Inc. to an organization designated by the sponsor. Frontage Laboratories Inc. will separately prepare a final report (one original copy), retain it, and submit its duplicate copy electronically to the sponsor. The sponsor will treat this final report as a source document. The investigator or subinvestigator will not be required to record it in the CRF.

7.2.5 Pharmacodynamic Evaluation

Blood will be sampled and processed in accordance with the following procedures, and the blood samples will be kept frozen until collection by the sample collecting facility. The sample collecting facility will extract DNA from the samples and transport the DNA packed in dry ice to the PD measurement laboratory.

1) Blood sampling
At each blood sampling timepoint, 10 mL of blood will be drawn into a tube containing EDTA. The tube will be slowly inverted 8 to 10 times to mix the blood with EDTA, and then kept frozen. The date of blood sampling will be documented in the medical records and CRF.
2) Blood sampling timepoints
At screening (the same schedule for all of the cohorts): any timepoint between the acquisition of informed consent and IMP administration on Day 1
Day 1, Day 8, Day 15, Day 22, and Day 29 of Course 1: predose. (Blood sampling scheduled for Day 1 can be performed during the screening examination period. On the day of IMP administration, blood should be collected before IMP administration.)
3) DNA extraction
The sample collecting facility will extract DNA after cryopreserving the sample.
4) Analysis of DNA methylation in LINE-1
DNA methylation in LINE-1 will be measured using the pyrosequencing assay validated by the PD measurement laboratory. Remaining samples after the measurement will be stored at the PD measurement laboratory until the sponsor instructs to discard them after the CSR is prepared.
Measurement results will be reported electronically by the PD measurement laboratory to an organization designated by the sponsor. The PD measurement laboratory will separately prepare a final report (one original copy), retain it, and

submit its duplicate copy electronically to the sponsor. This final report will be treated as a source document, and recording in the CRF is not required.

7.2.6 Investigational Medicinal Product Compliance

The investigator or subinvestigator will document the date and time of IMP administration, cohort, dose, and administration site in the medical records and CRF (or in the medical records during the extended treatment part). When the IMP is not administered at the timepoints stipulated in the protocol, the reason should be recorded in the CRF (or in the medical records during the extended treatment part).

7.3 Measures to Be Taken for Subjects Visiting or Planning to Visit Other Hospitals or Departments

At the time of obtaining informed consent, the investigator or subinvestigator will confirm whether or not the subject is receiving treatment at another hospital or department. If the subject is receiving treatment at another hospital or department, the investigator or subinvestigator will inform, with the subject's consent, the attending physician of that hospital or department about the subject's participation in the clinical trial and the IMP being used. The investigator or subinvestigator will also obtain and record in the CRF (or in the medical records during the extended treatment part) information on the treatment that the subject is receiving at the other hospital or department (name of disease being treated and information on the type of treatment or measures being implemented) and judge whether or not the subject should participate in the trial.

If a subject visits another hospital or department during the trial period, the investigator or subinvestigator will inform the attending physician of that hospital or department about the subject's participation in the clinical trial and the IMP being used. The investigator or subinvestigator will also obtain and record in the CRF (or in the medical records during the extended treatment part) information on the treatment that the subject receives at the other hospital or department (name of disease treated and information on the type of treatment or measures implemented) and judge whether or not the subject should continue to participate in the trial.

8 Adverse Events

8.1 Definitions

8.1.1 Adverse Event

(International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH] E2A guideline: Definition)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.[a]

For this trial, the term "medical product" is regarded as "IMP," and to secure the safety of subjects, AEs occurring from consent to the start of IMP administration are included in the definition of AEs in addition to the definition given by ICH.

If a disease, symptom, or sign existing at the time of acquisition of informed consent worsens after acquisition of informed consent, or if an AE occurring between the acquisition of informed consent and start of IMP administration worsens after administration of the IMP, the exacerbation will be treated as a new AE.

In this trial, however, progression (including relapse) of an underlying disease will not be treated as an AE. (If a symptom associated with progression [relapse] of an underlying disease corresponds to an "AE," the symptom will be evaluated as an AE.)

8.1.2 Serious Adverse Event

An SAE is defined as an AE corresponding to one of the events listed in 1) to 6) below.[a]

The seriousness of AEs occurring during the period from consent to the start of IMP administration will also be judged.

1) An event resulting in death
2) A life-threatening event
   The term "life-threatening" refers to an event in which the patient was at a risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, had it been more severe.

[a] "Clinical Safety Data Management", Notification No. 227 of the Examination Division, Pharmaceutical Affairs Bureau dated 20 Mar 1995 (ICH E2A).

3) An event requiring in-patient hospitalization or prolongation of existing hospitalization for treatment
4) An event resulting in persistent or significant disability/incapacity
5) An event causing a congenital anomaly/birth defect
6) A major event resulting in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but which may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in 1) to 5) above. Examples of such events are intensive treatment in an emergency room for bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Explanation of hospitalization for treatment of an SAE:

Hospitalization for treatment means that the subject must be hospitalized at a medical institution for treatment of an AE, typically for at least one night. This includes hospitalization for treatment of the AE in which no particular medical procedures are carried out (rest therapy). However, it does not include hospitalization for undergoing tests or treatment for an underlying disease or complication that has not worsened since the subject's entry into the trial, hospitalization for social reasons or convenience not intended for treatment of the AE, or hospitalization for treatment or tests scheduled prior to participation in the trial.

8.2 Response to Occurrence of Adverse Events

8.2.1 Actions to Be Taken for Subjects

The investigator or subinvestigator will provide adequate medical care for all clinically significant, trial-related AEs throughout the period of subject participation in the trial as well as thereafter. If treatment for an AE is necessary, the subject will be informed of this.

8.2.2 Expedited Reporting of Serious Adverse Events and Dose-limiting Toxicities

1) Serious Adverse Events
   a) Any SAEs occurring during the trial period regardless of causal relationship with the IMP
   b) Serious adverse events occurring during the follow-up period (see Section 8.4 Follow-up Investigation of Adverse Events), if a follow-up investigation is performed, for which a causal relationship with the IMP cannot be ruled out,[Note] or AEs that become serious during the follow-up period for which a causal relationship with the IMP cannot be ruled out [Note]

c) Among SAEs occurring after completion of the trial (after the follow-up investigation, if a follow-up investigation is performed) and reported by subjects to the investigator or subinvestigator, those for which the investigator or subinvestigator cannot rule out a causal relationship with the IMP [Note]

[Note] Including those for which a causal relationship is not determined.

2) Dose-limiting Toxicities

Any toxicity specified in Section 3.13.1 Trial Plan occurring during the DLT evaluation period (Course 1) will be reported.

3) Procedures for Expedited Reporting

a) When an AE falling under any of the above items (1) or (2) occurs, the investigator or subinvestigator will notify the sponsor promptly after becoming aware of the event (within 24 hours, in principle) in person, by telephone, or by e-mail (refer to Annex 1 Emergency Contact).

b) The investigator will then promptly submit a detailed report on any SAEs occurring after the start of IMP administration to the head of the trial site and the sponsor within 10 days after becoming aware of them using the report form of the trial site or sponsor. Any additional information will also be promptly relayed to the sponsor (within 24 hours, in principle) in person, by telephone, or by e-mail, and additional reporting will be performed if necessary.

c) When the investigator or subinvestigator is requested by the sponsor, the head of the trial site, or the IRB to prepare additional information (autopsy report, terminal care report, or other required information) on a reported SAE, the investigator or subinvestigator will respond to the request.

8.2.3 Expedited Reporting of Non-serious Adverse Events Resulting in Discontinuation of IMP Administration

When a non-serious AE occurs for which the investigator or subinvestigator judges that IMP administration should be discontinued (but not when IMP administration is merely temporarily interrupted), the investigator or subinvestigator will notify the sponsor within 3 working days in principle after their judgment in person, by telephone, or by e-mail (refer to Annex 1 Emergency Contact).

8.3 Assessment of Adverse Events

The investigator or subinvestigator will assess AEs for the following items.

8.3.1 Terms for Adverse Events

If the disease responsible for an AE can be specified, the name of the diagnosed disease will be recorded in the CRF (or in the medical records during the extended treatment part) and not the individual symptoms.

8.3.2 Date of Onset and Recovery

- Date of onset:
  The date of onset of an AE or date of confirmation of an AE will be recorded in the CRF (or in the medical records during the extended treatment part). If a disease, symptom, or sign existing at the time of acquisition of informed consent worsens, the date of exacerbation will be recorded in the CRF (or in the medical records during the extended treatment part) as "date of onset of AE." Also, if an AE occurring between the acquisition of informed consent and start of IMP administration worsens after administration of the IMP, the exacerbation will be recorded in the CRF (or in the medical records during the extended treatment part) as a new AE with the date of exacerbation recorded as "date of onset of exacerbated AE."
- Date of recovery:
  The date of recovery of an AE or date of confirmation of recovery of an AE will be recorded in the CRF (or in the medical records during the extended treatment part).

8.3.3 Severity (Grade)

Severity (grade) of AEs will be classified using the following five categories of Grades 1 to 5 in accordance with the CTCAE version 4.0.

In this trial, febrile neutropenia is defined as a neutrophil count below 500/μL accompanied by a fever of 38°C or higher.

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 ADL.[a]
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.[b]
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A semi-colon indicates "or" within the description of the grade.

[a]Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b]Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.3.4 Causal Relationship With Investigational Medicinal Product

The causal relationship between the IMP and AEs occurring after the start of IMP administration will be judged according to the following two categories.

1) Not related
   For reasons such as the following, the possibility of a relationship between occurrence of an AE and the IMP is not reasonably conceivable.

a) The event can be assumed to be caused by an underlying disease, complication(s), or previous disease(s).
b) The event can be assumed to be associated with age, sex, or some other demographic factor.
c) A temporal relationship between IMP administration and occurrence of the AE is unlikely.
   Example: An AE that occurs after a considerable lapse of time from the conclusion of IMP administration.
d) Considering the time course of the AE and IMP administration, a relationship with the IMP is unlikely.
   Example: Despite continuous administration of the IMP, the AE disappeared spontaneously without any treatment (except cases in which it is judged that the subject became habituated to the IMP during continued administration).
e) The event can be assumed to be caused by concomitant drug(s).
f) The event can be assumed to be incidental (such as an accident or incidental disease).
   Example: "femoral bone fracture" occurring in a traffic accident.
g) A relationship with the IMP can be ruled out for other reasons based on medical consideration.

2) Related

For reasons such as the following, the possibility of a relationship between occurrence of an AE and the IMP is reasonably conceivable.

a) A relationship is predictable from the pharmacological and toxicological effects of the IMP.
   Examples: Occurrence of "pancytopenia" when effects on the hematopoietic system have been observed in non-clinical studies, or the occurrence of "dehydration" when the drug has a diuretic effect.
b) The event has been observed in previous non-clinical studies and/or clinical studies.
   Example: An AE with high incidences in phase 1 studies.
c) A temporal relationship is suspected between IMP administration and onset of the AE.
   Example: "Allergic dermatitis" occurring several days after the start of IMP administration.
d) A relationship is suspected based on the outcome of an AE after discontinuation or dose reduction of the IMP.
   Example: Prompt disappearance of "nausea" after discontinuation of the IMP.
e) A relationship with the IMP cannot be ruled out for other reasons based on medical consideration.

8.3.5 Actions to Be Taken Regarding IMP Administration

Actions to be taken regarding IMP administration following the occurrence of an AE after initiation of IMP administration will be selected from among the following.

- No change
- Discontinuation of IMP administration
- Interruption of IMP administration
- Unknown
- Not applicable

8.3.6 Actions to Be Taken for Adverse Events

The performance of medical treatments (medications and/or other treatments) for AEs and details of the treatments will be described in the CRF (or in the medical records during the extended treatment part).

8.3.7 Outcome

The outcome of an AE will be selected from the following six categories (one only).

If the subject died, the date of death will be recorded in the CRF (or in the medical records during the extended treatment part); if the subject's condition was recovering/resolving, not recovered/not resolved, or unknown, the date of outcome confirmation will be recorded in the CRF (or in the medical records during the extended treatment part [Cohorts 1, 2, and 4]).

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered/resolved with sequelae
- Fatal
- Unknown (for some reason, a follow-up investigation could not be performed even once)

8.4 Follow-up Investigation of Adverse Events

The term "recovered" used below means that a subject who had an AE prior to the start of IMP administration returned to his or her original condition, or a subject who had an AE after the start of IMP administration returned to his or her condition before the start of IMP administration.

1) If an AE has not resolved by the end of the withdrawal examination, the investigator or subinvestigator will explain to the subject the need for post-trial follow-up investigation and request the subject's cooperation. The investigator or subinvestigator will conduct a follow-up investigation within 4 weeks after the end of the trial and record information regarding the AE in the subject's medical records. If an AE has not resolved by the end of the withdrawal examination, the investigator or subinvestigator will record the outcome in the CRF as "recovering/resolving," "not recovered/not resolved," or as otherwise appropriate.

2) If an AE has not resolved by the day of the follow-up investigation and a causal relationship with the IMP cannot be ruled out, [Note] follow-up investigation will be continued until the event resolves or becomes stable and information regarding the AE will be recorded in the subject's medical records. If a causal relationship between the AE and the IMP can be ruled out, no further follow-up will be made beyond the day of the initial follow-up investigation.
3) If, between the end of the withdrawal examination and the day of the follow-up investigation, a new SAE for which a causal relationship with the IMP cannot be ruled out [Note] occurs, or if an AE that has not resolved by the end of the withdrawal examination and for which a causal relationship with the IMP cannot be ruled out [Note] becomes serious, follow-up investigation will be conducted until the AE resolves or becomes stable and information regarding the AE will be recorded in the subject's medical records.
4) If an SAE for which a relationship with the IMP cannot be ruled out [Note] is discovered after the end of the withdrawal examination, or after the day of the initial follow-up investigation (if performed), follow-up investigation will be conducted until the AE resolves or becomes stable or until follow-up of the subject becomes impossible and information regarding the AE will be recorded in the subject's medical records.
5) If the treatment for AML is initiated after the end of the withdrawal examination, and it is difficult to confirm the subject's outcome under the influence of the treatment in the opinion of the investigator or subinvestigator, no follow-up investigation of the AE will be performed even if the subject has not recovered from the AE by the end of the withdrawal examination.

[Note] Including those for which a causal relationship is not determined.

8.5 Pregnancy

If women of childbearing potential or male subjects whose partners are capable of becoming pregnant participate in the trial, the investigator or subinvestigator will attend to the following.

- Information on pregnancy in the written information for subjects and ICF
- Explanation of contraceptive methods
- Reporting and follow-up of cases of pregnancy

8.5.1 Guidance to Subjects Including Contraceptive Methods

1) Before the start of the trial, the investigator or subinvestigator will explain to the subjects the importance of using contraception and the risks associated with pregnancy of a female subject or partner of a male subject and, after subjects have read the written information for subjects and understood it, the investigator or subinvestigator will have subjects sign the ICF.
2) If women of childbearing potential or male subjects whose partners are capable of becoming pregnant wish to participate in the trial, the investigator or

subinvestigator will instruct them to practice contraception during the period specified in the trial protocol.

3) Contraceptive methods include condoms, pills, pessaries, intrauterine device, implantable contraceptive devices [Note], spermicide [Note], vasectomy, and tubal ligation. However, if a female subject or male subject's partner is without question unable to become pregnant (ie, has undergone bilateral ovariectomy or hysterectomy or has not experienced menses for at least 12 consecutive months without an alternative medical cause, or the male subject/partner has undergone bilateral orchidectomy), use of contraception is unnecessary.
   [Note] Methods not approved or authorized in Japan.
4) The investigator or subinvestigator will instruct the subjects that if the contraceptive measures fail and evidence of pregnancy of the female subject or male subject's partner such as delay in menstruation is observed during the trial, this should be promptly reported to the investigator or subinvestigator.

8.5.2 Actions to Be Taken by the Investigator or Subinvestigator When Pregnancy Is Suspected

If the investigator or subinvestigator or a subject suspects that the subject has become pregnant before initiation of IMP administration, initiation of IMP administration will be withheld and a pregnancy test will be performed. If the test result is positive, the trial subject will be withdrawn without receiving IMP administration. If a pregnancy is suspected after initiation of IMP administration, IMP administration will be discontinued (refer to Section 9.2 Criteria and Procedures for Withdrawal of Individual Subjects).

8.5.3 Actions to Be Taken by the Investigator or Subinvestigator When a Subject Is Discovered to Be Pregnant

When a female subject is found to be pregnant, the investigator or subinvestigator will withdraw the subject from the trial and perform follow-up investigation until delivery or end of pregnancy, and report this in writing to the sponsor.

After discontinuation of IMP administration, the investigator or subinvestigator will perform the withdrawal examinations and follow-up observation stipulated in the protocol, in so far as they do not affect the pregnancy. For example, examinations such as radiography should not be performed even if they are stipulated in the protocol.

8.5.4 Expedited Reporting of Pregnancy

When a female subject or a partner of a male subject is found to be pregnant during the trial, the investigator or subinvestigator will promptly report this to the sponsor in person, by telephone, or by e-mail (refer to Annex 1 Emergency Contact). The investigator or subinvestigator will then provide any additional information requested by the sponsor.

8.5.5 Follow-up Investigation of Pregnancy

If a female subject becomes pregnant, the investigator or subinvestigator will perform follow-up investigation of the pregnancy up to delivery or the end of pregnancy and report the results of follow-up in writing to the sponsor. When a subject or subject's partner has delivered, it is best that the neonate be observed for at least 6 months after delivery.

9 Withdrawal of Individual Subjects From the Trial

Any subject may discontinue participation in the trial at any time without medical disadvantage. The investigator or subinvestigator may withdraw a subject from the trial at any time if it is considered necessary for medical treatment of that subject.

9.1 Screen Failure

If a subject is a screen failure, the following information should be recorded in the CRF for screen failure subjects.

Date of investigation (the start date of the screening examination), date of informed consent acquisition, date of birth, sex, reason for screen failure.

9.2 Criteria and Procedures for Withdrawal of Individual Subjects

In any of the events listed below, the investigator or subinvestigator will withdraw the subject from the trial, perform the tests such as the withdrawal examination stipulated in Section 7.1 Schedule and Procedures, and promptly inform the sponsor of the withdrawal (Annex 1 Emergency Contact). The investigator or subinvestigator will record the date and reason for withdrawal in the CRF.

For subjects who do not undergo the withdrawal examination, the date of withdrawal will be the day when the investigator or subinvestigator deems withdrawal is necessary.

If withdrawal is necessitated by problems with safety, such as the occurrence of an AE or aggravation of the underlying disease, the investigator or subinvestigator will promptly take appropriate measures and perform follow-up if necessary (refer to Section 8.4 Follow-up Investigation of Adverse Events).

1) Apparent progression (including the relapse) of the primary disease.
2) Dose-limiting toxicity that does not improve to the baseline level or show improvement by at least 1 grade within 4 weeks, or occurrence of another DLT.
3) Delay in commencement of the next course by more than 4 weeks due to an AE, unless the investigator or subinvestigator judges that continuation of SGI-110

administration is in the patient's best interest, in which case the delay may be extended by another 2 weeks.

4) Subject becomes pregnant.
5) Subject wishes to withdraw from the trial.
6) The investigator or subinvestigator judges that it is difficult to continue IMP administration due to occurrence of an AE.
7) The investigator or subinvestigator judges that it is necessary to discontinue IMP administration for any other reason.

9.3 Follow-up Investigation of Subjects Who Do not Visit the Trial Site

When a subject fails to visit the trial site and the reason is unknown, the investigator or subinvestigator will immediately contact the subject or their family by telephone or other means to confirm whether or not AEs have occurred and encourage the subject to return. If again the subject fails to visit the site after being contacted, the following information should be obtained and recorded in the CRF (or in the medical records during the extended treatment part).

1) The date of investigation
2) The method of investigation
3) Whether or not the subject was contacted
4) Reason why the subject does not (or cannot) visit the trial site
5) Occurrence or non-occurrence of AEs. If an AE has occurred: name of the event, date of onset and date of recovery, seriousness, severity, relationship to the IMP, measures taken regarding IMP administration, outcome.
6) If follow-up investigation is impossible: the reason why

10 Collection of Case Report Form Data and Specification of Source Data

10.1 Collection of Case Report Form Data

1) Electronic Data Capture (EDC) will be used in the primary evaluation part of the trial, and the paper CRF will be used in the extended treatment part for data collection.
2) Subject data will be entered directly into the database from the trial site via a Web browser. These data collected by EDC will constitute the CRF. The 12-lead ECG analysis results obtained from the ECG reading facility (central ECG reading facility) will be transferred from the ECG measurement facilities directly to the sponsor.
3) Regarding quality assurance of CRFs, the guidelines specified in "Use of Electromagnetic Records and Electronic Signatures in Applications for Approval or Licensing of Drugs" (PFSB Notification No. 0401022, dated 01 Apr 2005) and

"Guidance on Electronic Capture of Clinical Study Data" (Drug Evaluation Committee, Japan Pharmaceutical Manufacturers Association, dated 01 Nov 2007) will be observed

4) For every subject who provides consent to participate in the trial, a CRF will be created on an EDC data entry screen that conforms to the items of CRF data collection described in the trial protocol.
5) The investigator, subinvestigator, or trial associate will create CRFs according to the manual provided by the sponsor. If source documents are available and the objectivity of the data can be ensured, then the data may be recorded in a CRF by a trial associate.
6) When entering data into CRFs from the trial site, a predetermined check will be automatically performed. The investigator, subinvestigator, or a trial associate will make corrections as necessary.
7) The sponsor will verify CRFs in comparison to source documents and conduct data reviews. If additional query is necessary, the sponsor will issue an intra-system query and the investigator, subinvestigator, or a trial associate will perform data correction or provide a response to the sponsor's query as necessary.
8) A history of all revisions made after the initial data entry is saved on the server will be automatically recorded within the system (date and time of revision, name of person making revision, pre- and post-revision data, reason for revision, date and time of query, name of person issuing query, details of query, etc).
9) After completion of all CRF data entry and confirmation that the content is correct and complete, including confirmation of the audit trail, the investigator will attach an electronic signature.
10) Details concerning data collection will be specified in a separate manual prepared in advance.

10.2 Source Documents

1) Source documents are defined as those documents that are the source of data transcribed into CRFs as trial results.
Medical records and other records (medical records, nursing records, prescription records), registration verification forms, subject screening list, ICFs, clinical laboratory test and other measurement reports, ECG charts, IMP management records, and other documents
2) The investigator or the trial site will retain all trial-related documents and records except CRFs in such a manner that enables the sponsor or the regulatory authority to have direct access to the documents and records.
3) The original ICFs will be retained according to the method specified by each trial site.
4) After completion of the trial, the sponsor will retain the original CRFs on CD-ROM or some other appropriate electronic medium and the investigator or the trial site will retain copies.
5) The original report on results of drug concentration measurement will be kept by the laboratory performing drug concentration measurements, and the original

report on results of PD measurements will be kept by the PD measurement laboratory; copies will be kept by the sponsor.

10.3 Case Report Form Items to Be Treated as Source Data

Of the data recorded in the CRF, the following items will be treated as CRF-based source data.

- Investigator's signature, date of the investigator's confirmation
- Comments presented for each item
- Occurrence or non-occurrence of AEs. If an AE has occurred: name of the event, severity, seriousness, measures taken regarding IMP administration, treatment of AE, outcome, (causal) relationship to the IMP
- Reason for withdrawal
- Response to previous treatment
- Presence or absence, dose and regimen, and reason for use of concomitant drugs
- Presence or absence, details, and reason for implementation of concomitant therapies
- Cause of death found in an investigation on the outcome of survival

10.4 Data to Be Collected by the Sponsor

1) CRFs (data following acquisition of informed consent)
2) Clinical laboratory results and reference values
3) Copies of results of drug concentration measurement
4) Copies of results of PD measurement
5) Copies of ECG charts
6) 12-lead ECG analysis report

11 Statistical Analysis

The analysis sets, endpoints, analysis subjects, analysis methods, and other relevant matters in the primary evaluation part are defined in this section. Planned statistical analyses are detailed in the statistical analysis plan and PK analysis plan prepared separately. The statistical analysis plan and PK analysis plan will be finalized before database lock.

11.1 Statistical Analysis Sets

11.1.1 Safety Analysis Set

The safety analysis set will include subjects who have received at least one dose of the IMP.

11.1.1.1 Dose-limiting Toxicity Analysis Set

The DLT analysis set will include subjects in whom tolerability has been assessed in Cohorts 1 to 4 (subjects who have received all doses and completed all assessments scheduled for the DLT evaluation period).

11.1.2 Efficacy Analysis Set

The efficacy analysis set will include subjects who have received at least one dose of the IMP and have data of the efficacy endpoints after the start of IMP administration.

11.1.3 Pharmacokinetic Analysis Set

The PK analysis set will include subjects whose plasma drug concentrations have been measured.

11.1.4 Pharmacodynamic Analysis Set

The PD analysis set will include subjects in whom the extent of DNA hypomethylation in LINE-1 has been measured.

11.2 Handling of Data

1) Acceptable time windows of timepoints for examinations
   The acceptable time windows of timepoints for examinations to be used in tabulation are detailed in the statistical analysis plan.
2) Handling of missing data
   How to handle missing data is described in the statistical analysis plan.
3) Handling of events and censoring
   In the analysis of overall survival, all deaths (regardless of cause) will be defined as events, and time to death from the start date of IMP administration will be analyzed. If subjects are alive at the end of the primary evaluation part, they will be censored (the day of survival confirmation will be the day of censoring).

11.3 Analysis Items and Method

11.3.1 Safety Analysis

11.3.1.1 Primary Endpoint

1) Definition
   DLT

2) Analysis set
   DLT analysis set

3) Analysis method
Dose-limiting toxicities (by preferred term [PT]) occurring during Course 1 in each cohort will be tabulated (number and percentage of subjects with DLTs).

11.3.1.2 Secondary Endpoints

1) Definitions
   a) AEs
   b) Clinical laboratory values
   c) Vital signs (blood pressure, pulse rate, and body temperature) and body weight
   d) ECOG PS
   e) Twelve-lead ECG
   f) Chest X-ray

2) Analysis set
Safety analysis set

3) Analysis method
   a) Adverse events
   The following tabulations will be performed for each cohort:
      - All AEs occurring after the start of IMP administration (treatment-emergent adverse events) (all events, SOCs, and PTs) will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA).
      - Adverse events will be summarized (number and percentage of subjects with AEs) by CTCAE grade.
      However, if an event occurs more than once in the same subject, the most severe episode will be included in the tabulation.
      - Adverse events in treated subjects in each course will be summarized (number and percentage of subjects with AEs) by timing of occurrence.
      - Deaths, other SAEs, and AEs leading to discontinuation will be summarized.
      - Adverse drug reactions (AEs assessed as related to the IMP) will be summarized in the same manner as AEs.
      - Dose-limiting toxicities (including events occurring after the start of Course 2) will be summarized (number and percentage of subjects with DLTs).
   b) Clinical laboratory values
   Hematological and blood biochemistry data at each timepoint will be summarized by cohort as follows:
      - Descriptive statistics of measurements
      - Descriptive statistics of change from baseline

- A shift table of the value at the last evaluation and the worst value after the treatment relative to the baseline value by CTCAE grade

Urinalysis data at each timepoint will be summarized by cohort as follows:

- A shift table of the value at the last evaluation and the worst value after the treatment relative to the baseline value by CTCAE grade

c) Vital signs (blood pressure, pulse rate, and body temperature) and body weight
Vital signs (blood pressure, pulse rate, and body temperature) and body weight at each timepoint will be summarized by cohort as follows:

- Descriptive statistics of measurements
- Descriptive statistics of change from baseline

d) Eastern Cooperative Oncology Group performance status
Eastern Cooperative Oncology Group PS at each timepoint will be summarized by cohort (the number and percentage of subjects for each score).

e) Twelve-lead electrocardiogram
Heart rate, PR interval, RR interval, QRS interval, QT interval, and QTcF interval, at each timepoint will be summarized by cohort as follows:

- Descriptive statistics of measurements
- Descriptive statistics of change from baseline

QTcF interval at the last evaluation and the worst value (maximum value after the start of treatment) will be summarized by cohort.

- The number and percentage of subjects with a measured value > 450 ms, > 480 ms, or > 500 ms will be calculated.
- The number and percentage of subjects with change > 30 ms or > 60 ms will be calculated.

Assessment of ECG abnormalities (normal or abnormal) at each timepoint will be summarized by cohort as follows:

- A shift table of data from baseline

f) Chest X-ray
Assessment of chest X-ray abnormalities (normal or abnormal) at each timepoint will be summarized by cohort as follows:

- A shift table of data from baseline

11.3.2 Efficacy Analysis

1) Definitions
   a) Evaluation of the complete remission rate (CR), composite complete remission rate (CR + CRi + CRp), and overall remission rate (CR + CRi + CRp + PR) based on the response criteria for AML treatment established by an international working group (with partial modifications)
   b) Composite complete remission duration
   c) Overall survival

2) Analysis set
Efficacy analysis set

3) Analysis methods
   a) Remission
   Data will be summarized by cohort as follows:
      - Assessment in each course (CR, CRp, CRi, PR, no response, progressive disease, or NE)
      - Distribution of the best overall response: complete remission rate (CR), composite complete remission rate (CR + CRi + CRp), and overall remission rate (CR + CRi + CRp + PR)

   b) Composite complete remission duration
   Descriptive statistics of time from the first composite complete remission to relapse will be calculated for subjects who have achieved composite complete remission.

   c) Overall survival
   A Kaplan-Meier plot will be generated for each cohort that includes at least 6 treated subjects.

11.3.3 Pharmacokinetic Analysis

1) Analysis items
   a) SGI-110 and decitabine plasma concentrations
   b) Pharmacokinetic parameters for SGI-110 and decitabine in plasma
   Day 1: C_{max}, C_{max}/D, AUC_{24h}, AUC_{24h}/D, AUC_t, AUC_t/D, AUC_∞, AUC_∞/D, t_{max}, λ_z, AUC_%Extrap, $t_{1/2,z}$, CL/F, CL/F/BW, V_z/F, $V_z/F/BW$, and t_{last}
   Day 5 (Cohorts 1, 2, and 4) or Day 12 (Cohort 3): C_{max}, C_{max}/D, AUC_{24h}, AUC_{24h}/D, t_{max}, λ_z, $t_{1/2,z}$, CL/F, CL/F/BW, V_z/F, $V_z/F/BW$, and t_{last}
   c) AUC ratio of decitabine to SGI-110
      - Day 1: AUC_∞ and AUC_t
      - Day 5 (Cohorts 1, 2, and 4): AUC_{24h}
      - Day 12 (Cohort 3): AUC_{24h}
   d) Accumulation of SGI-110 and decitabine
      - $R_{5,ac}$ (AUC_{24h}) and $R_{5,ac}$ (C_{max}) (Cohorts 1, 2, and 4)
      - $R_{10,ac}$ (AUC_{24h}) and $R_{10,ac}$ (C_{max}) (Cohort 3)
   e) Non-linearity after multiple dosing of SGI-110 and decitabine
      - Ratio of AUC_{24h} on Day 5 (Cohorts 1, 2, and 4) or Day 12 (Cohort 3) to AUC_∞ on Day 1

2) Analysis set
PK analysis set

3) Calculation methods

- C_{max}, AUC_{24h}, AUC_t, AUC_∞, t_{max}, λ_z, AUC_%Extrap, $t_{1/2,z}$, t_{last}, CL/F, and V_z/F will be calculated by non-compartmental analysis using a PK analysis software for individual subjects.
- CL/F/BW and V_z/F/BW will be calculated by dividing CL/F and V_z/F by baseline body weight (kg), respectively.
- C_{max}/D, AUC_{24h}/D, AUC_t/D, and AUC_∞/D will be calculated by dividing C_{max}, AUC_{24h}, AUC_t, and AUC_∞ by the SGI-110 dose (mg/m^2), respectively.
- For AUC_{24h}, AUC_t, and AUC_∞ ratios of decitabine to SGI-110, the AUCs (ng·h/mL) calculated from their respective mass concentrations (ng/mL) will be converted to a molar basis, and the molar AUC of the metabolite will be divided by the molar AUC of SGI-110.
- $R_{5,ac}$ (AUC_{24h}) and $R_{5,ac}$ (C_{max}) will be calculated by dividing AUC_{24h} and C_{max} on Day 5 by AUC_{24h} and C_{max} on Day 1. $R_{10,ac}$ (AUC_{24h}) and $R_{10,ac}$ (C_{max}) will be calculated by dividing AUC_{24h} and C_{max} on Day 12 by AUC_{24h} and C_{max} on Day 1.
- The ratio of AUC_{24h} on Day 5 to AUC_∞ on Day 1 will be calculated by dividing AUC_{24h} on Day 5 by AUC_∞ on Day 1. The ratio of AUC_{24h} on Day 12 to AUC_∞ on Day 1 will be calculated by dividing AUC_{24h} on Day 12 by AUC_∞ on Day 1.

4) Statistical analysis methods
Descriptive statistics of the items mentioned in a) of 1) in Section 11.3.3 will be calculated by blood sampling timepoint, compound, and dose. Descriptive statistics of the items mentioned in b) of 1) in Section 11.3.3 will be calculated by compound and dose. Descriptive statistics of the items mentioned in c) of 1) in Section 11.3.3 will be calculated by dose. Descriptive statistics of the items mentioned in d) and e) of 1) in Section 11.3.3 will be calculated by compound and dose. Descriptive statistics to be calculated will be the number of subjects, arithmetic mean, standard deviation, coefficient of variation, minimum, median, and maximum for plasma drug concentrations and the number of subjects, arithmetic mean, standard deviation, coefficient of variation, geometric mean, minimum, median, and maximum for parameters other than plasma drug concentrations.

11.3.4 Pharmacodynamic Analysis

1) Item
Extent of DNA hypomethylation in LINE-1

2) Analysis set
PD analysis set

3) Analysis methods
Descriptive statistics of the extent of DNA hypomethylation in LINE-1 (percent change in the extent of DNA methylation from baseline) at each timepoint will be calculated by cohort.
Also, descriptive statistics of the extent of maximum DNA hypomethylation in LINE-1 (at the timepoint when a percent reduction from baseline is maximum) will be calculated.

11.3.5 Demographic and Other Baseline Characteristics

1) Definition
Age, sex, height, body weight, BSA, ECOG PS, diagnosis of AML, duration of illness, the presence or absence of hematopoietic stem cell transplantation for AML, the presence or absence of radiation therapy for AML, the presence or absence of other prior treatments for AML, karyotype at screening, the presence or absence of cytogenetic abnormalities, the presence or absence of extramedullary lesions after the diagnosis of AML, the proportion (maximum) of blast cells (leukemia cells) in the bone marrow after the diagnosis of AML, and baseline WBC count, neutrophil count and platelet count.

2) Analysis set
Safety analysis set (other analysis sets if necessary)

3) Analysis method
Calculation of frequency tabulation or descriptive statistics will be made by cohort according to the characteristics of each item.

11.4 Procedures for Reporting Deviations From the Original Statistical Analysis Plan

When it is necessary to amend the statistical analysis plan, the timing, details, and reason for the amendment will be documented in the CSR.

11.5 Rationale for Target Number of Patients

For Cohorts 1, 2, and 4, tolerability will be evaluated in at least 3 subjects per cohort based on the Guidelines for Clinical Evaluation of Antimalignant Tumor Drugs. If DLTs are evaluated in 3 subjects in a cohort for the recommended dose and regimen, additional subjects will be enrolled for further safety evaluation in 6 subjects. For Cohort 3, tolerability will be evaluated in 6 subjects.

12 Quality Control and Quality Assurance for the Trial

To ensure quality of the trial, trial sites, contract research organizations, laboratory performing drug concentration measurements, PD measurement laboratory, laboratories performing clinical tests, and the sponsor will perform quality control for the trial according to their respective Standard Operating Procedures.

The audit division of the sponsor company will carry out audits within the company and, as necessary, at the trial site and contract research organizations or organizations entrusted to perform related activities, and check whether quality control of the trial is appropriately performed according to the Standard Operating Procedures.

13 General Items of Caution Pertaining to the Trial

13.1 Ethics and Good Clinical Practice Compliance

This clinical trial is to be conducted in compliance with the ethical principles of the Declaration of Helsinki, the Pharmaceutical Affairs Law, the Ordinance on Good Clinical Practice (Ministry of Health and Welfare Ordinance No. 28 dated 27 Mar 1997), relevant notifications, and this trial protocol.

13.2 Institutional Review Board

Prior to performance of this trial, the appropriateness of performance of this trial will be reviewed from ethical, scientific, and medical perspectives by the IRB designated by the trial site, and this trial will be commenced only after obtaining the approval of the IRB.

13.3 Subject Consent

13.3.1 Procedures for Obtaining Consent

1) Prior to the start of the screening examination, the investigator or subinvestigator will fully explain the matters listed in Section 13.3.2 to each subject who will be included in the trial, using the written information for subjects and ICF, and give these documents to the subject. The subject will be provided sufficient time to make a decision regarding participation. After confirming that the subject has properly understood the explanation, the investigator or subinvestigator will obtain written voluntary consent for participation in the trial from the subject.
2) The investigator or subinvestigator who has provided the explanation and the subject will each put their printed name and personal seal or signature on the ICF, and write the date on which they sign or stamp the form. If a trial associate has provided a supplemental explanation of the trial, he/she will also put his/her printed name and personal seal or signature on the form and write the date on which he/she signs or stamps the form.

3) The original of the ICF that was signed or stamped and dated will be retained by the investigator or subinvestigator according to the regulations of the trial site. A copy of the original ICF will be given to the subject.
4) After obtaining informed consent from a subject, the investigator or subinvestigator will write the date of informed consent acquisition and subject identification code in the documents for enrolled subjects (list of screened subjects and list of enrolled subjects).
5) If new information becomes available that may influence the willingness of the subject to continue participation in the trial, the investigator or subinvestigator will promptly inform the subject of such information and confirm the willingness of the subject to continue participation in the trial, and then record the result in the subject's medical records. If there is guidance regarding the recording of re-consent stipulated by the trial site, it will be followed.
6) The investigator or subinvestigator will confirm the willingness of the subject to continue treatment in Course 2 and subsequent courses and obtain his/her consent between the visit on Day 22 of Course 1 and the start of Course 2.
7) The investigator or subinvestigator will confirm the willingness of the subject to receive the IMP in the extended treatment part and obtain his/her consent before the start of a treatment course in the extended treatment part.

13.3.2 Contents of Written Information for Subjects and Informed Consent Form

1) An explanation that the trial involves research
2) The type of IRB that reviews the appropriateness of trial conduct, matters to be reviewed by the IRB, and other relevant descriptions of the activity of the IRB
3) The objectives of the trial
4) The trial procedures (including research-related aspects of the trial, inclusion criteria for subjects, and, if random allocation is performed, the probability of randomization to each treatment arm)
5) The expected duration of the subject's participation in the trial
6) The planned number of subjects involved in the trial
7) The foreseeable IMP-related physical and mental benefits (if no benefits are expected, this should be indicated) as well as risks or inconveniences to the subject
8) The existence of alternative treatments for the subject, and their important potential benefits and risks
9) The treatment and compensation available to the subject in the event of trial-related injury to health
10) An explanation that the subject's participation in the trial is voluntary, and that the subject can refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which he or she would otherwise be entitled

11) An explanation that the subject will be informed in a timely manner if information becomes available that may be relevant to his or her willingness to continue participation in the trial
12) The circumstances or reasons under which the subject's participation in the trial should be terminated
13) An explanation that the monitors, the auditors, the IRB, and the regulatory authorities will be granted direct access to the subject's original medical records without violating the confidentiality of the subject, and that by signing the ICF, the subject is authorizing such access
14) An explanation that if the results of the trial are published, the subject's identity will remain confidential
15) The anticipated expenses to the subject for participating in the trial
16) The anticipated payment, if any, to the subject for participating in the trial (agreements on payment, etc)
17) The name, position, and contact address of the investigator or subinvestigator
18) The persons at the trial site to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury to health
19) Matters to be observed by subjects

13.3.3 Amendments to the Written Information for Subjects or Informed Consent Form

If revision of the written information for subjects or ICF becomes necessary due to newly obtained information, the investigator will promptly revise the written information for subjects or ICF to include that information after conferring with the sponsor.

The investigator, when revising the written information for subjects or ICF, will report this to the head of the trial site and submit the revised document to the IRB designated by the trial site to obtain its approval.

If new information becomes available that may influence the willingness of subjects to continue participation in the trial and the written information for subjects or ICF has been revised according to the new information, the investigator or subinvestigator will again obtain subjects' written informed consent to continue participation in the trial.

13.4 Management of Investigational Medicinal Products

1) The sponsor will issue the "Procedures for Handling of Investigational Medicinal Products" to the persons designated by the trial site.
2) The sponsor will issue the "Document on Investigational Medicinal Products Storage Conditions" to the investigator or subinvestigator, trial associates, and IMP manager.
3) The sponsor will deliver the IMPs to the trial site following the start of the trial period contracted with the trial site.

4) The IMP manager will manage the IMPs appropriately according to the "Procedures for Handling of Investigational Medicinal Products" prepared by the sponsor.
5) The IMP manager will prepare and retain the "Record of Management and Storage of Investigational Medicinal Products."

13.5 Direct Access to Source Documents and Monitoring

13.5.1 Direct Access to Source Documents

The head of the trial site and the investigator must accept monitoring and audits to be performed by the sponsor and inspection by the IRB and Japanese and foreign regulatory authorities, and must make source documents and all other trial-related records available to these agencies for direct access (including copying). Subjects authorize such direct access by signing the written ICF.

13.5.2 Monitoring

The sponsor bears responsibility for ethical, legal, and scientific conduct of the trial. The sponsor will perform monitoring according to the "Procedures for monitoring" specified for this trial. Monitoring includes periodic visits, phone calls, or other contact with the trial site for the provision, obtaining, and recording of updated trial-related information by monitors designated by the sponsor.

The sponsor may entrust a portion of monitoring activity to a contract research organization.

13.5.3 Documents to Be Retained by the Investigator

The trial-related documents to be retained by the investigator will be kept in the investigator's file, which will be managed by the investigator.

13.6 Deviations From and Changes or Amendments to the Trial Protocol

13.6.1 Deviations From the Trial Protocol

1) The investigator or subinvestigator should not deviate from the protocol or change it without prior written agreement between the investigator and the sponsor and the written approval of the IRB of the trial site based on prior review.
2) In unavoidable medical circumstances such as the need to avoid emergent risk to a subject, the investigator or subinvestigator may deviate from the protocol or change the protocol without prior written agreement from the sponsor and prior approval of the IRB. In such an event, the investigator will promptly submit a document providing the details of and reason for the deviation or change to the sponsor and the head of the trial site and obtain approval from the IRB. In

addition, the investigator will obtain written approval from the head of the trial site and the written agreement of the sponsor by way of the head of the trial site.

3) The investigator or subinvestigator will record all deviations from the protocol.

13.6.2 Amendments to the Trial Protocol

1) The investigator will promptly submit to the sponsor, the head of the trial site, and the IRB by way of the head of the trial site, a written report on any changes in the trial that may significantly affect conduct of the trial or increase risks to the trial subjects.
2) The sponsor, after conferring with the investigator, will agree with the investigator on the contents of the revised protocol and compliance with the revised protocol.
3) The sponsor will promptly submit the revised protocol to the head of the trial site.

13.7 Archiving of Records

1) The trial site will retain all the trial-related documents and records for the period of time indicated in a) or b) below, whichever is longer. However, if the sponsor requires a longer period of archiving, the head of the trial site will consult with the sponsor on the period and procedures of record retention.
   a) The date an Application for Approval of a Pharmaceutical Product for the IMP is granted; or, if the head of the trial site receives notification from the sponsor that development has been terminated or that results of the trial will not be submitted with the approval application, the date 3 years after receipt of such notification.
   b) The date 3 years after termination or completion of the trial.
2) The investigator will retain the trial-related documents and records as directed by the head of the trial site.
3) If it becomes no longer necessary to retain the trial-related documents and records at the trial site, the sponsor will notify the head of the trial site.

13.8 Termination or Interruption of Part or All of the Trial

13.8.1 Termination or Interruption of the Trial at Individual Trial Sites

1) In the event of termination or interruption of the trial, the investigator will promptly provide the head of the trial site with written notification and a written explanation of the details of the termination or interruption of the trial.
2) When the sponsor has been informed by the head of a trial site that the investigator has terminated or interrupted the trial, the sponsor will obtain a detailed written explanation of the termination or interruption of the trial from the head of the trial site.

13.8.2 Termination or Interruption of the Entire Trial

1) When the entire trial is to be terminated or interrupted by the sponsor, the sponsor will promptly provide the heads of all trial sites involved in the trial and the

regulatory authority with written notification and a detailed written explanation of the reason for the termination or interruption of the trial.

2) When the investigator has received notification of termination or interruption of the entire trial by the sponsor from the head of the trial site, the investigator will obtain a detailed written explanation of the termination or interruption of the trial from the head of the trial site, promptly notify the trial subjects currently receiving IMP administration, and take necessary measures such as switching to appropriate alternative treatment(s).
3) When development of the IMP is terminated by the sponsor, the sponsor will promptly provide the heads and the investigators of all trial sites involved in the trial and the regulatory authority with written notification and a detailed written explanation of the reason for the termination of development.

13.9 Protection of Subjects' Personal Information

In completion and handling of CRFs, the investigator and subinvestigator will take adequate care to ensure protection of the personal information of subjects. Individual subjects will be identified by subject numbers and subject identification codes. The sponsor will not provide the information obtained to any third party.

13.10 Compensation for Injury to Health

Trial subjects will be compensated for health damages according to the criteria established by the trial sponsor with reference to the "Guidelines for Health Damage Compensation to Trial Subjects" (revised 25 Nov 2009) of the Japan Pharmaceutical Industry Legal Affairs Association. Compensation for this trial will comprise medical costs and medical benefits.

13.11 Agreement on Publication

The sponsor may use the findings obtained from this trial for purposes such as an "Application for Approval of a Pharmaceutical Product" for the IMP.

When the results of this trial and relevant data are to be published in scientific journals or at academic meetings, the investigator will obtain prior written approval from the sponsor.

14 Trial Administrative Structure

The administrative structure of this trial is shown in Annex 1, Annex 2, and Annex 3.

15 Scheduled Duration of the Trial

Overall trial duration: 01 Oct 2014 to 31 Dec 2019

1) Cohorts 1, 2, and 4
(Primary Evaluation Part [Cohorts 1, 2, and 4])

01 Oct 2014 to 31 May 2016

(Extended Treatment Part [Cohorts 1, 2, and 4])

01 Jun 2016 to 31 Dec 2019

2) Cohort 3
(Primary Evaluation Part [Cohort 3])

01 Sep 2016 to 30 Nov 2017

(Extended Treatment Part [Cohort 3])

01 Dec 2017 to 31 Dec 2019

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