Synopsis

Clinical Report Synopsis for Protocol 343-14-001

Name of Sponsor: Otsuka Pharmaceutical Co., Ltd.

Name of Investigational Medicinal Product: SGI-110

Protocol Title: A Phase 1, Multicenter, Open-label Study to Evaluate the Tolerability of SGI-110 in Japanese Patients With Acute Myeloid Leukemia

Principal or Coordinating Investigator and Trial Centers: This trial was conducted at 5 trial sites in Japan.

Publications: None to date.

Trial Period:

Date of first signed informed consent: 07 Jan 2015

Date of last trial observation: 31 May 2019

Clinical Development Phase: 1

Trial Interruption: There was no unplanned trial interruption.

Scientific Background and Explanation of Rationale:
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 for the treatment of myelodysplastic syndrome (MDS) including chronic myelomonocytic leukemia and in the European Union for the treatment of acute myeloid leukemia (AML) in patients.
It is believed that when DNA methylation occured 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.
SGI-110 is resistant to be metabolized by cytidine deaminase, the enzyme that degrades decitabine. 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.
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 for which no standard therapy has been established.

Objectives:

Primary objective:

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

Secondary objectives:

- To perform PK evaluation of plasma SGI-110 and decitabine
- To evaluate efficacy; complete remission (CR) rate, composite complete remission (CR + complete remission with incomplete blood count recovery [CRi] + complete remission with incomplete platelet recovery [CRp]) rate, overall remission (CR + CRi + CRp + partial remission [PR]) rate, overall survival (OS), CR + CRi + CRp duration
- To evaluate safety through observed adverse events (AEs) and examinations

Exploratory objective:

- To perform pharmacodynamic (PD) evaluation of the extent of DNA hypomethylation

Methodology:

Each course consisted of 4 weeks (28 days). In Cohorts 1, 2, and 4, subjects received SGI-110 once daily for 5 consecutive days (Day 1 to Day 5), followed by a 23-day nondosing period (Day 6 to Day 28). In Cohort 3, subjects received SGI-110 once daily for 10 days in total (SGI-110 was 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 was suspended for 16 days (Day 13 to Day 28). The sponsor confirmed the incidence of dose-limiting toxicity (DLT) during the DLT evaluation period in each cohort and judged 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 was ≥2/3 or ≥2/6, then there was no transition to the next cohort, and the maximum tolerated dose (MTD) was 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 did not reach either ≥2/3 or ≥2/6 in any of the cohorts in the table above, the MTD was not determined in this trial. For Cohort 3, DLT was evaluated but the MTD for 10-day regimen was not determined from the incidence of DLT.

The DLT evaluation period was for the duration of Course 1. Subjects who completed investigational medicinal product (IMP) administration and all observations during the DLT evaluation period, and who did not have any apparent progression of AML, were permitted to continue treatment with IMP following the DLT evaluation period if they wished.

The primary evaluation data for Cohorts 1, 2, and 4 had a cutoff date of 31 May 2016 and the data for Cohort 3 had a cutoff date of 30 Nov 2017. The period up until the data cutoff was defined as the primary evaluation part. This was followed by an extended treatment part to assess long-term safety, which included those subjects on IMP treatment who had consented to participate in the extended treatment part. Transition from the primary evaluation part to the extended treatment part took place at the start of the next course after the data cutoff. The extended treatment part data had a cutoff date of 31 May 2019.

Number of Subjects:
Planned: Maximum: 24 subjects

- Cohort 1: 3 to 6 subjects
- Cohort 2: 3 to 6 subjects
- Cohort 3: 6 subjects
- Cohort 4: 3 to 6 subjects

Screened: 15 subjects
Enrolled and treated: 21 subjects

- Cohort 1: 4 subjects
- Cohort 2: 6 subjects
- Cohort 3: 7 subjects
- Cohort 4: 4 subjects

Diagnosis and Main Criteria for Inclusion:
Patients meeting all of the following main criteria at the time of screening were included in this trial:
Male or female patients with a diagnosis of AML (World Health Organization [WHO] classification 2008).

- Patients, 20 years of age or older, who were unresponsive to standard chemotherapy or had relapsed following standard chemotherapy
- Patients, 65 years of age or older, who were not eligible for standard intensive chemotherapy and who met 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 was unrelated to AML
  - Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2
  - 75 years of age or older

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration, and Lot Numbers:

1) Test product:
   SGI-110 for injection: A glass vial contains SGI-110 equivalent to 100 mg of free acid, as a lyophilized powder.
   SGI-110 diluent for reconstitution: A glass vial contains 1.2 or 3 mL of custom diluent for reconstitution.
2) Dose and mode of administration:
   The total daily dose was determined based on the subject's body surface area calculated from height and weight prior to administration in each course, according to the treatment cohort.
   SGI-110 was administered SC.
   The dose and regimen for each cohort was as follows:
   - Cohort 1 (36 mg/m^2, 5-day regimen)
   - Cohort 2 (60 mg/m^2, 5-day regimen)
   - Cohort 3 (60 mg/m^2, 10-day regimen)
   - Cohort 4 (90 mg/m^2, 5-day regimen)
3) Lot numbers:
   - SGI-110 for injection: 140045, 150027, 16E11, 17I023
   - SGI-110 diluent for reconstitution: 130089, 140065, 16B22/2, 17G04

Reference Product, Dose, Dosage Regimen, Formulation, Mode of Administration, and Lot Numbers:

Not applicable.

Duration of Treatment:

In Cohorts 1, 2, and 4, subjects received SGI-110 once daily for 5 consecutive days (Day 1 to Day 5), followed by a 23-day nondosing period (Day 6 to Day 28). One course consisted of 4 weeks (28 days).
In Cohort 3, subjects received SGI-110 once daily for 10 days in total (SGI-110 was 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 was suspended for 16 days (Day 13 to Day 28). One course consisted of 4 weeks (28 days).

Trial Assessments:

Efficacy:

- Response criteria: Bone marrow aspiration and peripheral blood testing
- Overall survival: The date of final survival confirmation

Pharmacokinetics: The collection of blood samples

Pharmacodynamics: The collection of blood samples

Safety: Dose limiting-toxicities, AEs, clinical laboratory values (hematology test, blood biochemistry test, and urinalysis), vital signs (blood pressure, pulse rate, and body temperature), body weight, ECOG PS, 12-lead electrocardiogram (ECG), and chest X-ray

Criteria for Evaluation:
Efficacy: Complete remission rate, CR + CRi + CRp rate, CR + CRi + CRp + PR rate, OS, and CR + CRi + CRp duration

Pharmacokinetics: Plasma concentrations of SGI-110 and decitabine, and these PK parameters

Pharmacodynamics: Extent of DNA hypomethylation in long interspersed nucleotide element-1 (LINE-1)

Safety: Primary endpoint was DLT. Secondary endpoints were AEs, clinical laboratory values (hematology test, blood biochemistry test, urinalysis), vital signs (blood pressure, pulse rate, body temperature), body weight, ECOG PS, 12-lead ECG, and chest X-ray.

Pharmacokinetic/Pharmacodynamic Methods:
Bioanalytical: Plasma samples were analyzed for SGI-110 and decitabine using validated high-performance liquid chromatography method with tandem mass spectrometric detection.

Pharmacokinetics: Plasma concentrations of SGI-110 and decitabine were analyzed using noncompartmental methods.

Pharmacodynamics: DNA samples were analyzed to determine the extent of inhibition of DNA methylation in LINE-1 by using validated pyrosequencing assay method.

Statistical Methods:
Determination of Sample Size: For Cohorts 1, 2, and 4, tolerability was evaluated in at least 3 subjects per cohort based on the Guidelines for Clinical Evaluation of Antimalignant Tumor Drugs. If DLTs were evaluated in 3 subjects in a cohort for the recommended dose and regimen, additional subjects were enrolled for further safety evaluation in 6 subjects. For Cohort 3, tolerability was to be evaluated in 6 subjects.

Subject Samples: Subject samples identified for this trial included the efficacy analysis set, the PK analysis set, the PD analysis set, the DLT analysis set, and the safety analysis set.

Efficacy Analysis Set: The efficacy analysis set included subjects who had received at least one dose of IMP and had data of the efficacy endpoints after the start of IMP administration.

Pharmacokinetic Analysis Set: The PK analysis set included subjects whose plasma drug concentrations had been measured.

Pharmacodynamic Analysis Set: The PD analysis set included subjects in whom the extent of DNA hypomethylation in LINE-1 had been measured.

Dose-limiting Toxicity Analysis Set: The DLT analysis set included subjects in whom tolerability had been assessed in Cohorts 1 to 4 (subjects who had received all doses and completed all assessments scheduled for the DLT evaluation period).

Safety Analysis Set: The safety analysis set included subjects who had received at least one dose of the IMP. The safety analysis set was mainly used for presentations of safety data except DLT.

Efficacy: Remission (CR, [CR + CRi + CRp], and [CR + CRi + CRp + PR]) based on the response criteria for AML treatment established by an international working group (with partial modifications) and composite complete remission duration were summarized using descriptive statistics by cohort. Overall survival was summarized using a Kaplan-Meier plot by cohort.

Pharmacokinetics/pharmacodynamics: The PK and PD data were summarized by descriptive statistics, respectively.

Safety: Dose-limiting toxicity occurring during Course 1 in each cohort were tabulated (number and percentage of subjects with DLTs). Adverse events were summarized in terms of number and percentage of subjects experiencing an AE by cohort. Safety variables were summarized using descriptive statistics or shift tables.

Summary of Results:
Disposition, Demographics, and Baseline Characteristics:
Subject Disposition:
Course 1 (DLT evaluation period):
A total of 25 subjects with AML who signed informed consent and were screened in this trial; 21 subjects were enrolled and treated with IMP at least once. Nineteen subjects completed Course 1 (DLT evaluation period). There were 2 subjects who discontinued from this trial before completion of Course 1. The reason for discontinuation was clear progression of the primary disease including relapses (one of the 4 subjects in each of the 36- and 90-mg/m^2 on the 5-day regimens).
Course 2 or later (extended treatment period):
A total of 16 subjects transited in the extended treatment period. There were 13 subjects who discontinued from this trial. The reason for discontinuation was clear progression of the primary disease including relapses (2 on the 36-mg/m^2 5-day regimen, 2 on the 60-mg/m^2 5-day regimen, 1 on the 90-mg/m^2 5-day regimen, and 3 on the 60-mg/m^2 10-day regimen), delay in commencement of the next course by more than 4 weeks (1 on the 60-mg/m^2 5-day regimen), subject's wish to withdraw from this trial (1 on the 60-mg/m^2 10-day regimen), and occurence of AE (2 on the 60-mg/m^2 5-day regimen and 1 subject on the 60-mg/m^2 10-day regimen).

Demographics, and Baseline Characteristics:

5-day regimen:

Of the 14 subjects, 4 subjects were male and 10 subjects were female. The overall median age was 74.0 years (range: 49 to 85 years). The ECOG PS was 0 for 5 subjects (35.7%), 1 for 8 subjects (57.1%), and 2 for 1 subject (7.1%). The disease status was de novo AML in 8 subjects (57.1%) and secondary AML in 6 subjects (42.9%). Eleven of the 14 subjects (78.6%) had previously received chemotherapy for AML.

10-day regimen:

Of the 7 subjects, 5 subjects were male and 2 subjects were female. The overall median age was 74.0 years (range: 71 to 85 years). The ECOG PS was 0 for 2 subjects (28.6%), 1 for 5 subjects (71.4%), and 2 for 0 subject (0.0%). The disease status was de novo AML in 3 subjects (42.9%) and secondary AML in 4 subjects (57.1%). All of the 7 subjects (100.0%) had previously received chemotherapy for AML.

Efficacy Results:

- One subject had CRi on the 90 mg/m^2 5-day regimen; the time to response was 26 days, and the composite complete remission duration was 188 days.
- One subject achieved CR on the 60-mg/m^2 10-day regimen. The time to response was 29 days, and the CR duration was 152 days.
- Two subjects had CRi on the 60-mg/m^2 10-day regimen. One subject had 208 days in the time to response and 39 days in the composite complete remission duration, and the other subject had 93 days in the time to response and 4 days in the composite complete remission duration.

Pharmacokinetic/Pharmacodynamic Results:

- The mean C_{max} and AUC of both SGI-110 and decitabine increased dose dependently following both single and multiple administration of SGI-110 at 36, 60, and 90 mg/m^2.
- SGI-110 and decitabine did not accumulate by administration of SGI-110 once daily for 5 consecutive days or once daily for 10 days (on Days 1 to 5 and Days 8 to 12).
- SGI-110 and decitabine showed linearity in multiple administration of SGI-110, with the AUC_{24h} for multiple dosing comparable to AUC_{∞} for single dosing.
- The median t_{max} of SGI-110 and decitabine ranged respectively from 0.97 to 1.51 hours and from 1.27 to 2.04 hours following single and multiple administration of SGI-110.
- The mean $t_{1/2,z}$ of SGI-110 and decitabine ranged respectively from 0.503 to 0.833 hours and from 0.821 to 1.14 hours following single and multiple administration of SGI-110.
- The mean AUC ratio of decitabine to SGI-110 ranged from 0.721 to 1.03 following single and multiple administration of SGI-110.
- The mean % DNA LINE-1 demethylation-time profile showed the same kinetics and the maximum % DNA LINE-1 demethylation was observed on Day 8 at all doses on the 5-day regimen.

- The maximum % DNA LINE-1 demethylation was observed on Day 15 on the 10-day regimen.
- The individual maximum % DNA LINE-1 demethylation ranged from −21.40 to −1.66 on the 5-day regimen and from −29.00 to −6.71 on the 10-day regimen.

Safety Results:

5-day regimen:

- No subjects had DLT at any dose level.
- All of the 14 subjects with AML experienced treatment-emergent adverse events (TEAEs).
- Investigational medicinal product-related TEAEs were reported in 12 subjects (85.7%).
- Grade ≥3 TEAEs of were reported in 13 subjects (92.9%).
- The most common Grade ≥3 TEAEs were lymphocyte count decreased (50.0%; 7/14), febrile neutropenia (42.9%; 6/14), platelet count decreased and white blood cell count decreased (35.7%; 5/14 each), and neutrophil count decreased (28.6%; 4/14).
- No deaths were reported during the treatment period.
- Nine subjects experienced serious adverse events (SAEs); 2 subjects experienced SAEs related to IMP.
- Three subjects experienced TEAEs leading to discontinuation of IMP; these TEAEs were not related to IMP.
- The most commonly reported TEAEs related to injection site events were injection site induration and injection site pain, each occurring in 3 subjects (21.4%). No Grade ≥3 injection site events were reported.
- No clinically significant findings were observed in vital signs, body weight, 12-lead ECGs or chest X-ray.

10-day regimen:

- One of the 6 subjects had DLT, and the DLT was Grade 4 neutrophil count decreased (non-serious) that was not resolved within 7 days.
- All of the 7 subjects with AML experienced TEAEs.
- Investigational medicinal product-related TEAEs were reported in 5 subjects (71.4%).
- Grade ≥3 TEAEs were reported in 7 subjects (100.0%).
- The most common Grade ≥3 TEAEs were lymphosyte count decreased (85.7%; 6/7); platelet count decreased (71.4%; 5/7); white blood cell count decreased (57.1%; 4/7); and neutrophil count decreased (28.6%; 2/7).
- No deaths were reported during the treatment period.
- Four subjects experienced SAEs; 1 subject experienced SAEs related to IMP.

- Two subjects experienced TEAEs leading to discontinuation of IMP; these TEAEs were not related to IMP.
- The most commonly reported TEAEs related to injection site events were injection site pain, injection site reaction, and injection site vesicles, each occurring in 1 subject (14.3%). No Grade ≥3 injection site events were reported.
- No clinically significant findings were observed in vital signs, body weight, 12-lead ECGs, or chest X-ray.

Conclusions:

This trial evaluated the tolerability of SGI-110 when administered SC to Japanese patients with AML.

SGI-110 SC injection was generally well tolerated at 36, 60, and 90 mg/m^2 (5-day) and 60 mg/m^2 (10-day) in Japanese subjects with AML. No significant safety concerns were identified in this trial.