Clinical Study Protocol — SGI-110-04

A Phase 3, Multicenter, Open-label, Randomized Study of SGI-110 versus Treatment Choice (TC) in Adults with Previously Untreated Acute Myeloid Leukemia (AML) Who Are Not Considered Candidates for Intensive Remission Induction Chemotherapy

PROTOCOL TITLE PAGE

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Study Acknowledgement

A Phase 3, Multicenter, Open-label, Randomized Study of SGI-110 versus Treatment Choice (TC) in Adults with Previously Untreated Acute Myeloid Leukemia (AML) Who Are Not Considered Candidates for Intensive Remission Induction Chemotherapy

Version 2.0, 6 March 2015

This protocol has been approved by Astex Pharmaceuticals, Inc. The following signature documents this approval.

[redacted] [redacted]
Signature

March 7, 2015
Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. Further, I agree to conduct this study in accordance with Good Clinical Practice and applicable regulatory requirements.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Astex Pharmaceuticals, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (printed)	Signature
Date	Study Center Number
Institution Name	Center Location: City, State or Province, Country

Please forward the original signed Protocol Acceptance Statement to Astex Pharmaceuticals, Inc.
Retain a copy of this form with the study protocol in your regulatory file.

PROTOCOL APPROVAL PAGE

A Phase 3, Multicenter, Open-label, Randomized Study of SGI-110 versus Treatment Choice (TC) in Adults with Previously Untreated Acute Myeloid Leukemia (AML) Who Are Not Considered Candidates for Intensive Remission Induction Chemotherapy

Version 2.0, 6 March 2015

QA Approval:

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PROTOCOL SYNOPSIS

Study Number and Title:
SGI-110-04: A Phase 3, Multicenter, Open-label, Randomized Study of SGI-110 versus Treatment Choice (TC) in Adults with Previously Untreated Acute Myeloid Leukemia (AML) Who Are Not Considered Candidates for Intensive Remission Induction Chemotherapy

Investigational Drug: SGI-110 for subcutaneous (SC) injection

Clinical Phase: 3

Study Centers Planned/Country: Multicenter global study (approximately 100-160 centers)

Study Objectives:
Primary Objective

- To assess and compare efficacy (complete response [CR] rate and overall survival [OS]) between SGI-110 and TC in adults with previously untreated AML who are not considered candidates for intensive remission induction chemotherapy.

Secondary Objectives

- To assess and compare effects of SGI-110 and TC in adults with previously untreated AML who are not considered candidates for intensive remission induction chemotherapy with respect to the following variables:
  - Composite CR (CRc = CR + Complete response with incomplete blood count recovery [CRi] + Complete response with incomplete platelet recovery [CRp]) rate.
  - Number of days alive and out of the hospital.
  - Progression-free survival (PFS).
  - Transfusion needs.
  - Health-related quality of life (QOL).
  - Duration of CR.
  - Safety.

Exploratory Objectives

- [redacted].
- [redacted]

Study Design and Investigational Plan:
Multicenter, randomized, open-label study of SGI-110 versus TC. Blinded central reading of bone marrow and disease response will be performed. Subjects will be adults with previously untreated AML who are unfit to receive and not considered candidates for intensive remission induction chemotherapy. Approximately 800 subjects will be randomly assigned (1:1) to 1 of 2 groups:

- SGI-110: 60 mg/m^2 SGI-110 given SC daily for 5 days (Days 1-5) in 28-day cycles.
- TC: subjects will be assigned (before randomization) by the investigator to 1 of the following treatment regimens:
  - 20 mg cytarabine given SC twice daily (BID) on Days 1-10 every 28 days.
  - 20 mg/m^2 decitabine given intravenously (IV) daily on Days 1-5 every 28 days.
  - 75 mg/m^2 azacitidine given IV or SC daily on Days 1-7 every 28 days.

Data will be reviewed by an independent Data Monitoring Committee (DMC) at regular intervals primarily to evaluate safety during study conduct. The co-primary endpoints are CR rate and OS. If either of the co-primary efficacy endpoints reaches statistical significance in favor of SGI-110 at either the interim analysis (OS only) or final analysis (CR and OS), then the study will be considered positive in efficacy. Randomization and analyses will be stratified by age, Eastern Cooperative Oncology Group (ECOG) performance status, study center region, and secondary AML or poor-risk cytogenetics.

Study Population:
Approximately 800 adults with previously untreated AML who are unfit to receive and not considered candidates for intensive remission induction chemotherapy at the time of enrollment, with the following criteria.

Inclusion Criteria
Subjects must fulfill all of the following inclusion criteria.

1. Able to understand and comply with study procedures, and provides written informed consent before any study-specific procedure.
2. Cytologically or histologically confirmed diagnosis of AML (except M3 acute promyelocytic leukemia) according to the 2008 World Health Organization (WHO) classification (bone marrow or peripheral blood blast counts ≥20%).
3. Performance status (ECOG) of 0-3.
4. Adults with previously untreated AML except for hydroxyurea or corticosteroids. Prior hydroxyurea or lenalidomide treatment for myelodysplastic syndrome (MDS) is allowed.
5. Unfit to receive or not considered candidates for intensive remission induction chemotherapy at time of enrollment based on EITHER:
   a. ≥75 years of age
      OR
   b. <75 years of age with at least 1 of the following:
      i. Poor performance status (ECOG) score of 2-3.
      ii. Clinically significant heart or lung comorbidities, as reflected by at least 1 of:
         1) Left ventricular ejection fraction (LVEF) ≤50%.
         2) Lung diffusing capacity for carbon monoxide (DLCO) ≤65% of expected.
         3) Forced expiratory volume in 1 second (FEV1) ≤65% of expected.
         4) Chronic stable angina or congestive heart failure controlled with medication.
      iii. Liver transaminases >3 × upper limit of normal (ULN).
      iv. Other contraindication(s) to anthracycline therapy (must be documented).
      v. Other comorbidity the investigator judges incompatible with intensive remission induction chemotherapy, which must be documented and approved by the study medical monitor before randomization.
6. Creatinine clearance as estimated by the Cockroft-Gault (C-G) or other medically acceptable formulas ≥30 mL/min.
7. Women of child-bearing potential must not be pregnant or breastfeeding and must have a negative pregnancy test at screening. Women of child-bearing potential and men with female partners of child-bearing potential must agree to practice 2 highly effective contraceptive measures during the study and for at least 3 months after completing treatment and must agree not to become pregnant or father a child while receiving treatment with SGI-110 and for at least 3 months after completing treatment.

Exclusion Criteria
Subjects meeting any of the following exclusion criteria will be excluded from the study:

1. Candidate for intensive remission induction chemotherapy at the time of enrollment.
2. Candidate for best supportive care only, ie, not a candidate for any active therapy with the TC comparators.
3. Known extramedullary central nervous system (CNS) AML.
4. Second malignancy currently requiring active therapy except breast or prostate cancer stable on or responding to endocrine therapy.
5. Prior treatment with decitabine or azacitidine.
6. Hypersensitivity to decitabine, azacitidine, cytarabine, SGI-110, or any of their excipients.
7. Treated with any investigational drug within 2 weeks of the first dose of study treatment.
8. Total serum bilirubin >2.5 × ULN, except for subjects with Gilbert's Syndrome for whom direct bilirubin is <2.5 × ULN, or liver cirrhosis or chronic liver disease Childs-Pugh B or C.
9. Known active human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infection. Inactive hepatitis carrier status or low viral hepatitis titer on antivirals is allowed.
10. Known significant mental illness or other condition such as active alcohol or other substance abuse or addiction that, in the opinion of the investigator, predisposes the subject to high risk of noncompliance with the protocol.
11. Refractory congestive heart failure unresponsive to medical treatment; active infection resistant to all antibiotics; or advanced pulmonary disease requiring >2 liters per minute (LPM) oxygen.

Study Treatment:

- SGI-110: 60 mg/m^2 SGI-110 given SC daily on Days 1-5 in 28-day cycles. Treatment should be given for at least 6 cycles in the absence of unacceptable toxicity or disease progression requiring alternative therapy. Beyond 6 cycles, treatment should continue as long as the subject continues to benefit based on investigator judgment.
- TC: before randomization, subjects will be assigned by the investigator to 1 of the following treatment regimens (dose, schedule, and administration route; other treatment parameters, such as duration of treatment and dose adjustment guidelines, should follow locally approved prescribing information and institutional standard practice):
  - 20 mg cytarabine given SC BID on Days 1-10 every 28 days.
  - 20 mg/m^2 decitabine given IV daily on Days 1-5 every 28 days.
  - 75 mg/m^2 azacitidine given IV or SC daily on Days 1-7 every 28 days.

Study Endpoints:

Co-primary Endpoints

- CR rate based on modified International Working Group (IWG) 2003 AML Response Criteria.
- OS, defined as the number of days from randomization to death.

Secondary Endpoints

- CRc (CR+CRi+CRp) rate.
- Number of days alive and out of the hospital.
- PFS, defined as the number of days from randomization to disease progression or death, whichever occurs first.
- Number of red blood cell (RBC) or platelet transfusions (units) over the duration of the study treatment.
- Health-related QOL by EQ-5D (consisting of the EQ-5D-5L descriptive system and the EQ Visual Analogue Scale [EQ VAS]).
- Duration of CR, defined as the time from first CR to time of relapse.
- Incidence and severity of adverse events (AEs).
- 30- and 60-day all-cause early mortality.

Study Assessments and Procedures:

A 14-day screening period is allowed (unless otherwise specified). After randomization, visits will occur on every treatment day. In addition, visits will occur on Days 8, 15, and 22 of the first 2 cycles of therapy and only on Day 15 in Cycles 3-6. In Cycles >6, only the treatment day visits are required, with hematology blood draws only on Day 1. Additional visits based on treatment effect and blood counts may be done at the investigator's discretion. Subjects will attend a safety follow-up visit after the last study treatment. For subjects who discontinue study treatment before Cycle 6, long-term follow-up visits will occur monthly until 6 months after the start of study treatment and then every 3 months thereafter. For subjects who discontinue study treatment after Cycle 6, long-term follow-up will be every 3 months.

Efficacy Assessments:

Peripheral blood (PB) will be assessed at baseline and on Day 1 of each cycle for response evaluation. Bone marrow (BM) aspirate/biopsy will be performed at screening and then at the end of Cycles 2, 4, and 6 unless PB shows persistence of leukemic blasts that excludes the possibility of a marrow response. After Cycle 6 BM assessment, BM aspirate/biopsy will be repeated every 3 months for the first year on study and then every 6 months thereafter until PB or BM assessment shows disease progression or relapse. Response evaluation will be based on BM blinded assessment and the most concomitant PB counts. After blinded BM response is confirmed, assessment of normal count recovery will be done based initially on the most concomitant PB and in later cycles on PB counts from Day 1 of each cycle to avoid transient treatment-induced normal count suppression.

Pharmacokinetic Assessments:

Sparse PK samples (as specified by the collection schedule) will be collected at selected centers for subjects receiving SGI-110 and for subjects in the TC group who receive decitabine IV. Blood samples will be collected after drug administration in Cycle 1 (SGI-110 and decitabine IV).

Biomarker Assessments:

Blood and BM samples will be collected at screening for AML verification, molecular genetics, and cytogenetics.

Health-related QOL Assessment:

EQ-5D 5 level (EQ-5D-5L) will be administered before treatment on Day 1 of each cycle and, for subjects who discontinue study treatment before Cycle 6, monthly until 6 months after the start of study treatment.

Safety Assessments:
Documented safety assessments will include AEs, concomitant medications, physical examination results, vital signs, electrocardiogram (ECG), ECOG performance status, hematology, and chemistry, according to the schedule of events. ECGs in triplicate will be conducted predose, 1-2 hours after Cycle 1 Day 1 dosing, and at study treatment discontinuation. Clinically significant abnormal ECG at study treatment discontinuation as compared to the predose ECG should be followed for recovery or stabilization.

Sample Size and Statistical Analyses:

Sample Size Calculation:
Assuming a CR rate of approximately 0.20 for subjects treated in the TC group and 0.30 or higher for subjects treated with SGI-110, 800 subjects (400 per treatment group) will have approximately 89% power to detect the overall difference of 0.10 at an alpha level of 0.04 using a 2-sided Cochran Mantel-Haenszel test.

For survival, an analysis at 670 death events will provide 90% power to detect a hazard ratio of approximately 0.78 (a difference in median survival of 7 months in the TC group versus 9 months in the SGI-110 group when using a 2-sided stratified log-rank test at a 0.05 alpha level. Accrual is expected to be uniform over a 21 month enrollment period (with an additional follow-up of 12 months), so the assessment of survival needs approximately the same sample size of 800 subjects. Primary response and survival analyses will be performed after 670 death events have occurred.

Efficacy:
The primary endpoint of CR rate will be compared between the 2 treatment groups using a Cochran Mantel-Haenszel test at an alpha level of 0.04 stratified by age (<75 or ≥ 75 years), ECOG performance status (0-1 or 2-3), study center region (North America, Europe, rest of world), and secondary AML or poor-risk cytogenetics (either, neither). The co-primary endpoint of OS will be displayed using a stratified Kaplan-Meier estimate and will be compared between the 2 treatment groups using a stratified log-rank statistic at an alpha level of 0.05 or 0.01 (depending on the CR test result), including the same stratification variables used for analysis of CR rate. If statistical significance is achieved for both CR rate and OS at targeted levels of significance, hierarchically the CRc rate, the number of days alive and out of the hospital (NDAOH), and PFS will be assessed. The CRc rate will be compared between the 2 treatment groups using the same method as for CR. The NDAOH will be evaluated using a 2-sample t-test. PFS will be evaluated using the same method as for OS.

Safety:
Safety will be assessed by subject-reported and investigator-observed AEs, physical examination, laboratory tests (hematology and chemistry), vital signs, and ECG. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) with severity categorization based on Common Terminology Criteria for Adverse Events (CTCAE) v4.03. Treatment exposure, AEs including relatedness and severity, serious AEs (SAEs), and reasons for treatment discontinuation will be tabulated and presented for all subjects who receive any amount of study treatment. Concomitant medication will be coded using WHO Drug Dictionary.

Formal Interim Analysis for Efficacy:
One interim analysis of OS is planned after approximately half of the required death events have occurred. This interim analysis will be conducted by an independent DMC, using the Lan-DeMets implementation of an O'Brien-Fleming boundary that will preserve an overall 2-sided 0.01 alpha level. The DMC will also perform regular data reviews with the main purpose of ensuring safety of study subjects and quality of trial conduct.

Study Duration:
The expected study duration is approximately 36 months including 21 months for completing enrollment and approximately 12-15 months follow-up before final analyses. The study is expected to start in Q1 2015.

Compliance Statement:
The study will be conducted in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, US Title 21 CFR Parts 11, 50, 54, 56, and 312; the EU Clinical Trials Directive and its successor; principles enunciated in the Declaration of Helsinki; and all human clinical research regulations in countries where the study is conducted.

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ABBREVIATIONS AND DEFINITIONS

ADL	activities of daily living
AE	adverse event
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AUC	area under the curve
BED	biologically effective dose
BID	twice daily
BM	bone marrow
BMT	bone marrow transplant
BSA	body surface area
CBC	complete blood count
CBF	core binding factor
CDA	cytidine deaminase
C-G	Cockroft-Gault
CI	confidence interval
CFR	Code of Federal Regulations
C_{max}	maximum concentration
CNS	central nervous system
CR	complete response
CRc	composite complete response (CR+CRi+CRp)
CRF/eCRF	case report form/electronic case report form
CRi	complete response with incomplete blood count recovery
CRp	complete response with incomplete platelet recovery
CTCAE	Common Terminology Criteria for Adverse Events
DLCO	diffusing capacity of the lung for carbon monoxide
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMEA	European Agency for the Evaluation of Medicinal Products
EQ-5D™	a standardized instrument for use as a measure of health outcome
EQ-5D-5L	EQ-5D 5 level health questionnaire
EQ VAS	EQ visual analog scale
FAB	French-American-British
FDA	Food and Drug Administration
FEV1	forced expiratory volume in the first second
FIH	first-in-human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCT	hematopoietic cell transplant
HCV	hepatitis C virus
HED	human equivalent dose
HIV	human immunodeficiency virus
HMA	hypomethylating agent
HNSTD	highest non-severely toxic dose
HR	hazard ratio
IB	Investigator Brochure

ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product (the specific Astex drug product under study)
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IWG	International Working Group
LDAC	low-dose Ara-C
LINE-1	long interspersed nucleotide element-1
LPM	liters per minute
LVEF	left ventricular ejection fraction
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MSDS	material safety data sheet
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NDAOH	number of days alive and out of the hospital
NOAEL	no observed adverse event level
NR	no response
OS	overall survival
OSHA	Occupational Safety and Health Administration
PB	peripheral blood
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamic(s)
PFS	progression-free survival
PK	pharmacokinetic(s)
PS	performance status
PT	preferred term
QOL	quality of life
QT	QT interval
QTc	heart rate corrected interval
RBC	red blood cells
ROW	rest of world
R/R	relapsed/refractory
RR	relative risk
SAE	serious adverse event
SC	subcutaneous
SEER	Surveillance, Epidemiology and End Results
SOC	system organ class
SSC	Study Steering Committee
STD_{10}	dose severely toxic to 10% of animals/rodents
SUSAR	serious unexpected suspected adverse reaction
TC	treatment choice
TEAE	treatment-emergent AE
TN	treatment-naïve
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

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1.0 INTRODUCTION AND BACKGROUND

1.1 Acute Myeloid Leukemia (AML) in Patients Who Are Not Considered Candidates for Intensive Remission Induction Therapy and the Elderly

Acute myeloid leukemia (AML) is a genetically heterogeneous group of cancers that have in common clonal proliferation and arrested differentiation of myeloid precursors. Incidence increases with age and is about 12 cases per 100,000 for those at and above the median age at diagnosis of 65 years (Schiffer and Anastasi 2014). Overall 5-year survival is 15% and varies substantially with age (Shah et al 2013). Patients age 70-79 years and over age 79 years have 5-year survival rates of 3% and 0%, respectively.

In a recent analysis of US Surveillance, Epidemiology and End Results (SEER) data, trends in relative survival by age were compared over 3 successive decades from 1977 through 2006 for 19,000 patients at least 65 years of age with AML (Thein et al 2013). Overall, survival improved for each successive decade in patients from 65-74 years old. In this age range, 12-month survival increased from 20% to 25% to 30% in the 3 successive cohorts. However, survival rates did not significantly improve in patients at least 75 years of age. The oldest old, at least 85 years of age, had the lowest survival, with no improvement. Thus, despite ongoing incremental improvements in both AML chemotherapy and supportive care since the mid-1970s, mortality following an AML diagnosis remains persistently high and without improvement in patients ≥75 years of age.

In addition to age, other adverse prognostic indicators in AML include poor performance status, adverse cytogenetic or molecular genetic findings, past exposure to cytotoxic or radiation therapy, and history of myelodysplasia or another hematologic disorder (Schiffer et al 2014). There is a correlation between age at diagnosis of AML and complex cytogenetic disease characteristics. Complex karyotype also correlates with disease resistance to therapy (Grimwade et al 2001). In summary, AML in patients who are not considered candidates for intensive remission induction chemotherapy, particularly elderly patients, remains a persistent unmet medical need.

For young patients, an AML diagnosis necessitates immediate intensive remission induction therapy. The goal is complete and prolonged disease remission. Yet for elderly patients with AML, intensive chemotherapy is often inappropriate due to adverse disease factors that cause chemo-resistance and comorbidities that exacerbate therapy-induced toxicity. Multivariate analyses in 2 retrospective series confirm that an unfavorable karyotype is an independent negative prognostic indicator in adults receiving induction chemotherapy (Kantarjian et al 2006; Kantarjian et al 2010).

Among 998 subjects age 65 years or older with AML or high-risk myelodysplastic syndrome (MDS) who received intensive chemotherapy between 1980 and 2004, independent negative prognostic indicators for complete response (CR), induction (8-week) mortality, and survival included age ≥75 years, unfavorable karyotype, Eastern Cooperative Oncology Group (ECOG) performance status (PS) 3 or 4, longer duration of antecedent hematologic disorder, treatment outside a laminar airflow room, and abnormal organ function (Kantarjian et al 2006).

A subsequent analysis focused on 446 subjects ≥70 years of age with AML (>20% blasts) treated with cytarabine-based intensive chemotherapy between 1990 and 2008 to identify risk groups for high induction (8-week) mortality. By multivariate analysis, risk factors for 8-week mortality (36%) after intensive chemotherapy included age ≥80 years, ≥3 cytogenetic abnormalities, ECOG PS ≥2, and serum creatinine >1.3 mg/dL (Kantarjian et al 2010). Additional series support these conclusions (Grimwade et al 2001, Appelbaum et al 2006, Knipp et al 2007). Thus, factors predicting failure of intensive induction chemotherapy in AML include elderly age, complex karyotype, and patient characteristics including performance status and organ function.

Recently, the Italian hematology groups published a consensus-based definition of unfitness for intensive chemotherapy that includes age >75 years, cardiac or pulmonary comorbidity, low performance status, and any other comorbidity judged by the physician to be incompatible with intensive chemotherapy (Ferrara et al 2013).

1.2 Treatment Options for Patients with AML Who Are Not Considered Candidates for Intensive Remission Induction Therapy

No standard therapy exists for patients with previously untreated AML who are not candidates for intensive remission induction chemotherapy. The National Comprehensive Cancer Network (NCCN), European Leukemia Net, and European Society for Medical Oncology all recommend possible treatments with low-dose Ara-C (LDAC), azacitidine, or decitabine in addition to enrolling patients in experimental treatment clinical trials.

Median overall survival in trials of these therapies varies from 5 to 25 months after initial diagnosis, depending on baseline subject features and therapy received (Fenaux et al 2010; Dombret et al 2014; Kantarjian, Thomas et al. 2012; Estey 2007). The most common Grade ≥3 AEs in all these trials are hematologic, including febrile neutropenia, neutropenia, thrombocytopenia, and anemia, with incidence from 20% to 94%. Thirty-day all-cause mortality ranged from 8% to 26%, and 60-day all-cause mortality ranged from 18% to 23%. Studies from which these results were derived are described individually below.

In a Phase 3 trial comparing LDAC to hydroxyurea in subjects with AML or high-risk MDS not considered fit for intensive treatment, LDAC led to an AML CR rate of 18% (compared with 1% for hydroxyurea) and improved survival (odds ratio 0.60; 95% confidence interval [CI] 0.44–0.81; p=.0009) (Burnett et al 2007). Similarly, a Phase 3 trial comparing azacitidine to conventional care in MDS subjects using French-American-British (FAB) criteria led to a CR rate of 18% in the subset of MDS subjects re-categorized as AML by World Health Organization

(WHO) criteria (blasts 20% to 30%; Swerdlow et al 2008) with azacitidine (compared with a CR rate of 16% with conventional care) and improved survival (median 24.5 months compared with 16.0 months, respectively) (Fenaux et al 2010). A more recent phase 3 study of azacitidine versus conventional care regimens (best supportive care, LDAC, or intensive chemotherapy 7+3 treatment) in 488 subjects showed no difference in CR rate and no statistically significant difference in overall survival (OS), although a trend toward OS improvement was evident for azacitidine (median survival of 10.4 months for azacitidine versus 6.5 months for conventional care regimens with a hazard ratio of 0.85, p=0.10) (Dombret et al 2014). Similarly, in a Phase 3 trial comparing decitabine to LDAC or best supportive care in 485 subjects ≥65 years of age with AML, decitabine in a 5-day regimen led to a CR rate of 16% (compared with 8% for LDAC) and improved survival at the final analysis (median 7.7 months compared with 5.0 months, respectively; nominal p=.037) (Kantarjian, Thomas et al 2012).

After the randomized study of the 5-day decitabine regimen in subjects with AML who were ≥65 years of age, multivariate analysis was performed to investigate effects of baseline characteristics on survival (Mayer et al 2014). Results were in general similar to those of retrospective series assessing factors predicting survival in elderly subjects undergoing intensive induction therapy for AML. Independent negative prognostic indicators included age ≥75 years, ECOG PS >1, poor cytogenetics, baseline blasts >50%, low baseline platelets, and high baseline white blood cell (WBC) counts. However, in contrast to results observed in patients receiving intensive chemotherapy, decitabine responses occurred across all risk groups. The authors conclude that response to decitabine was better than response to cytarabine or best supportive care and most clearly demonstrated in patients ≥75 years of age.

Health-related quality of life (QOL) evaluation is sparse in patients with AML. A 2008 review of QOL assessed in randomized, controlled trials in leukemia identified only 4 trials in AML that measured QOL and called for more QOL research (Efficace et al 2008). A recently published single-center trial evaluating QOL concluded that, in 92 AML survivors, QOL was worse than the QOL in the general population (Leunis 2014). Another trial evaluating QOL in 20 adults ≥60 years of age with AML suggested that complete remission was associated with improved global health, physical function, and role function (Alibhai 2009).

In AML, supportive care is also often used to maximize quality of life, while not necessarily prolonging life. Supportive care for AML is imprecisely defined and "generally refers to treatment with antibiotics, transfusions of blood and blood products, hydroxyurea, and hematapoietic growth factors" (Ritchie and Roboz 2010).

A recent retrospective report described the outcomes of 43 elderly patients with AML who were referred to palliative care (Cheng et al 2015). Of these 43 patients, about half received only supportive care after their AML diagnosis. Approximately half died in acute hospital settings, while about 30% died in palliative care settings. Over half spent their entire final month of life in a hospital, and infections accounted for more than half of the deaths overall. Median time from diagnosis to death was 9 months. Thus, life expectancy, harm, and quality of life appear to be similar to or worse with supportive care only, as compared with therapy. A separate review

article also suggests that any therapy is better than supportive care alone (Nazha and Ravandi 2014).

1.3 Summary of Nonclinical and Clinical Data for SGI-110

Please refer to the most recent Investigator Brochure (IB) for the complete and most up-to-date information.

1.3.1 SGI-110 Nonclinical Data Summary

1.3.1.1 Activity

SGI-110 is a dinucleotide of decitabine and deoxyguanosine, designed to protect the active decitabine moiety from inactivation by cytidine deaminase (Griffiths, Choy 2013). In vitro evidence suggests that SGI-110 has a longer half-life than decitabine in the presence of cytidine deaminase (Yoo et al 2007). SGI-110 has been investigated in a number of nonclinical studies for its pharmacodynamic effects on global DNA methylation and on the re-expression of specific genes that are silenced in cancer cells due to an altered methylation status of their DNA sequence. SGI-110 induced a dose-dependent decrease of proliferation and clonogenic survival in many different human cancer cell lines, including AML cell lines (Jueliger et al 2014, Srivastava et al 2014). These effects were associated with a decrease of global DNA and gene specific methylation. Re-expression of tumor suppressor genes like p16, p15, MLH1 and RASSF1A was also observed in xenografts at tolerated and efficacious regimens (Fang et al 2014).

1.3.1.2 Pharmacokinetics and Toxicology

Pharmacokinetic (PK) studies in nonclinical species showed that upon subcutaneous (SC) administration, SGI-110 converts to decitabine with species differences in conversion rates (slower in primates and faster in rodents). Conversion appears to occur in blood and plasma but may also occur intracellularly in tissues. SGI-110 is stable in hepatic microsomes and in incubations with hepatocytes. In the presence of cytosolic fractions, SGI-110 converted to decitabine. SGI-110 did not inhibit CYP 450 enzymes and is unlikely to cause drug-drug interactions mediated by CYPs. SGI-110 did not inhibit hERG channel activity in vitro at up to 300 μM.

Nonclinical toxicology of SGI-110 was evaluated initially over one 28-day cycle (plus recovery) in rats and rabbits. To support the intended Phase 3 regimen in the clinic, 3-cycle studies used the Daily×5 dosing schedule in rats and monkeys.

SGI-110 toxicity findings in rat and rabbit studies are similar to the nonclinical study findings of decitabine. Myelosuppression, thymus weight reduction, and testicular atrophy were the main study findings, similar to results in repeat-dose toxicity studies with decitabine in mice, rats, rabbits, and dogs. Myelosuppression and thymus toxicities were reversible during recovery periods, whereas testicular atrophy persisted for both SGI-110 and decitabine.

Myelosuppression, particularly neutropenia, has been reported as a dose-limiting toxicity (DLT) for decitabine in human clinical studies.

Additional non-GLP studies in cynomolgus monkeys showed that PKs of SGI-110 and decitabine were most representative of human PK data. Hematologic parameters from the 2-cycle non-GLP study in monkeys confirmed a profile consistent with the pharmacological action of SGI-110 in humans.

In the 3-cycle GLP toxicology study in rats, mortalities occurred at the higher dose levels of 40 mg/kg starting later in the second cycle and for 20 mg/kg later in the third cycle. The cause of these mortalities appeared to be opportunistic infections secondary to severe neutropenia. Decitabine exposures at SGI-110 dose levels of 20 and 40 mg/kg in rats were greater than 340- and 600-fold higher, respectively, than human clinical exposures after the 60 mg/m^2 dose. STD_{10} in rats was 20 mg/kg over 2 cycles and between 10 and 20 mg/kg over 3 cycles. Hematologic changes at all SGI-110 dose levels were reversible and consistent with the expected pharmacodynamic effect of SGI-110. Organ weight changes and/or other reversible microscopic changes were noted in the low-dose animals, including effects on testes, epididymides, thymus, spleen, and adrenal glands at dose levels of ≥5 mg/kg. Histologic changes were completely or partially reversible for all organs within a 28-day recovery period. Toxicokinetic exposures of decitabine observed in rats offer considerable margins relative to exposures at the proposed clinical Phase 3 dose of 60 mg/m^2. Relative to clinical exposures, the area under the curve (AUC) exposures in rats were ~90-fold higher at 5 mg/kg and more than 300-fold higher at the 2-cycle STD_{10} dose of 20 mg/kg.

In monkeys, the highest tested dose over 3 cycles was 4.5 mg/kg/dose (human equivalent dose [HED] 54 mg/m^2), which was found to be the no observed adverse event level (NOAEL). Highest non-severely toxic dose (HNSTD) was not identified in this study. Dose-dependent bone marrow (BM) hypocellularity was the main finding, which correlated with hematological changes. There were no clinical signs or macroscopic findings; no effects on body weight or food consumption; and no effects on ophthalmologic, electrocardiographic, serum chemistry, and urinalysis parameters. Hematologic and histologic changes in BM at all SGI-110 dose levels were reversible and consistent with the expected pharmacologic effect of SGI-110. Possible SGI-110-related injection site changes of hyperkeratosis at Day 85 and residual inflammation following a 28-day dose-free recovery were noted for individual animals at the highest dose tested (4.5 mg/kg). Toxicokinetic exposures (AUC) in monkeys at the NOAEL dose of 4.5 mg/kg/dose were in the range of AUCs observed in the clinic after 60 mg/m^2, the recommended Phase 3 dose.

In summary, the main effect observed in nonclinical toxicology evaluation of SGI-110 was BM suppression, consistent with its intended pharmacological action.

1.3.2 SGI-110 Clinical Data Summary

Study SGI-110-01 was a first-in-human (FIH) study in subjects with MDS or AML. It was conducted in 2 phases and enrolled approximately 400 subjects:

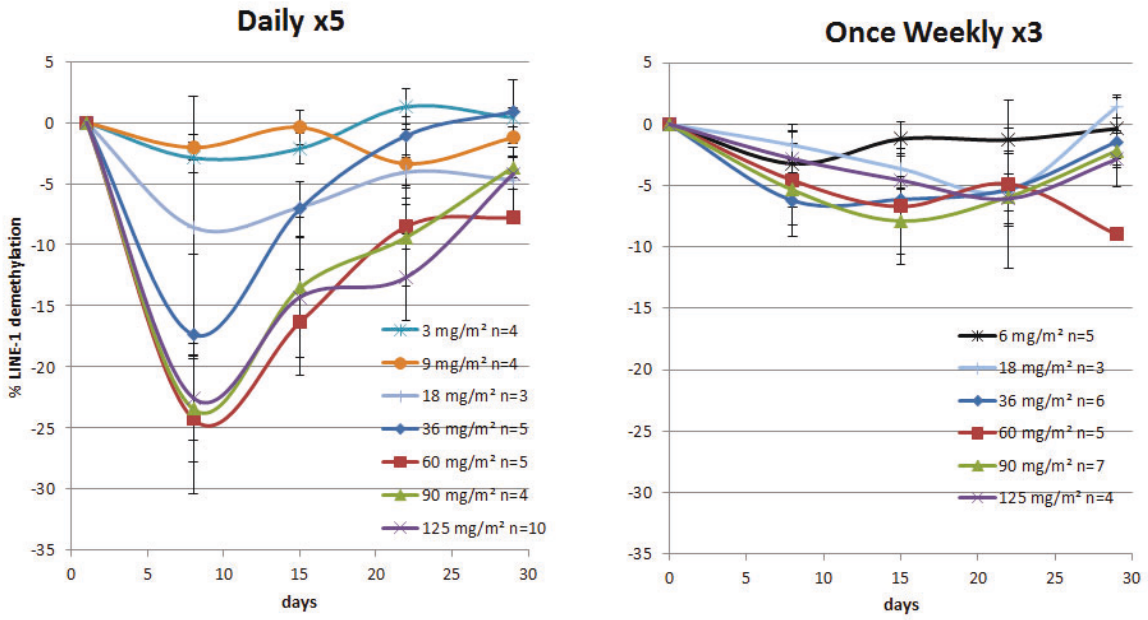
- Phase 1 Dose Escalation in 93 subjects established the maximal tolerated dose (MTD) and biologically effective dose (BED) based on long interspersed nucleotide element-1 (LINE-1) demethylation. LINE-1 demethylation relative to baseline in peripheral blood mononuclear cells (PBMC) provides a reliable surrogate of global hypomethylation by hypomethylating agents (HMAs). Phase 1 tested 28-day regimens of SGI-110 of (1) once daily for the first 5 days (Daily×5) or (2) once weekly for 3 weeks. LINE-1 demethylation was greater for the Daily×5 regimen. Subsequently, a third 28-day regimen was studied: twice weekly SGI-110 for 3 weeks.
- Phase 2 Dose Expansion in over 300 subjects established response rate and safety in different subject populations of MDS and AML using 3 different doses/regimens. Five-day regimens of 60 and 90 mg/m^2/day were tested in both AML and MDS subjects. After safety and activity were established with the 5-day regimen, a single-arm 10-day regimen with 60 mg/m^2/day was studied in AML subjects.

1.3.2.1 Phase 1 (SGI-110-01 Dose Escalation)

Dose escalation was in subjects with refractory or relapsed MDS or AML who had ECOG PS 0-2 and acceptable liver and kidney function (Kantarjian, Roboz et al 2012). Co-primary endpoints were MTD and BED; results are described below.

- MTD
  - Daily×5 MTD was reached for MDS subjects at 90 mg/m^2/day but was not reached for AML subjects up to 125 mg/m^2. Of 12 subjects enrolled at the 125 mg/m^2 dose level, 3 had MDS, and 9 had AML. Although none of the subjects with AML experienced DLT, 2 of 3 subjects with MDS treated at 125 mg/m^2 Daily×5 experienced DLTs (febrile neutropenia + bacteremia in 1 subject, and febrile neutropenia + thrombocytopenia + fatal sepsis in another subject).
  - The MTD was not reached for the once weekly (up to 125 mg/m^2/dose) or the twice weekly (up to 90 mg/m^2/dose) regimens.
- BED (defined as the minimum dose that achieves maximal demethylation of LINE-1 from 3 successive cohorts)
  - The Daily×5 regimen had the greatest effect on LINE-1 demethylation, and the BED was 60 mg/m^2/day (Figure 1). Similar LINE-1 demethylation occurred at 60, 90, and 125 mg/m^2.
  - Less demethylation was observed with the Once Weekly regimen; the Twice Weekly regimen did not lead to better LINE-1 demethylation than the Daily×5 regimen.

Figure 1: LINE-1 Demethylation Results from the Dose Escalation Part of SGI-110-01 Using 2 Regimens



Source: Kantarjian, Roboz et al 2012

A total of 74 subjects with relapsed/refractory AML were treated with SGI-110 in the Phase 1 dose escalation segment. Responses were observed starting at the 36 mg/m^2 dose level (Table 1). Of 49 subjects treated at 36 mg/m^2 or higher in the daily and weekly regimens, 5 CRc (CR + complete response with incomplete blood count recovery [CRi] + complete response with incomplete platelet recovery [CRp]), including 2 CRs, were observed. Three of 5 responses occurred with the 60 mg/m^2/day dose.

Table 1: Heavily-pretreated AML Responses and Characteristics (Phase 1)

Subject	Dose (mg/m^2)	# Prior Regimens / Prior BMT	Prior HMA Exposure (prior response)	Response to SGI-110
[redacted]	36	1 / No	No	CRi
	60	4 / Yes	Decitabine (UNK)	CR
	60	5 / Yes	No	CR
	60	4 / No	Decitabine (NR) Azacitidine (NR)	CRi
	125	6 / No	No	CRp

BMT: BM transplant; HMA: hypomethylating agent; NR: no response; CR: complete response; CRi: CR with incomplete blood count recovery; CRp: CR with incomplete platelet recovery; UNK: unknown.

Source: Roboz et al 2013; data on file

In summary, Phase 1 showed that the Daily×5 regimen induced maximal DNA demethylation, and the dose of 60 mg/m^2/day Daily×5 was the BED. The 90 mg/m^2/day Daily×5 regimen was the highest well-tolerated dose for both MDS and AML subjects. Once weekly and twice weekly regimens were well tolerated at all doses but did not improve biological or clinical activity relative to the Daily×5 regimen.

1.3.2.2 Phase 2 (SGI-110-01 Dose Expansion)

Phase 2 dose expansion was opened as a multicenter, open-label, randomized dose-response comparison of 60 vs 90 mg/m^2 SGI-110 SC Daily×5. Subjects were stratified by disease type (treatment-naïve elderly AML, relapsed/refractory AML, treatment-naïve MDS, and relapsed/refractory MDS). Approximately 50 subjects were enrolled for each disease cohort. The 60 mg/m^2 Daily×5 dose was chosen because it represented the BED from Phase 1, while 90 mg/m^2 was chosen to explore benefit from a higher dose that was still well tolerated in both MDS and AML subjects. After safety and preliminary efficacy were established with the Daily×5 regimen, a 10-day regimen with 60 mg/m^2/day was studied in AML, first in relapsed/refractory subjects and then in treatment-naïve elderly subjects.

1.3.2.2.1 Treatment-naïve Elderly AML

Eligibility for treatment-naïve elderly subjects with AML in Study SGI-110-01 Phase 2 is defined below. Each eligibility criterion is recognized as high risk for more intensive therapy (Estey 2007). In addition to being ≥65 years of age, study subjects must have met at least one of these criteria:

- Secondary AML.
- Poor-risk cytogenetics (monosomies or partial deletions of chromosome 5 or 7, abnormalities of 3q or 11q, translocation (6p23;9q34) or (9q34;22q11.2), or at least 3 unrelated cytogenetic abnormalities of any kind).
- Pre-existing clinically significant 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), unrelated to leukemia.
- Poor ECOG PS of 2.

Subjects were first randomly assigned to either 60 or 90 mg/m^2/day SGI-110 Daily×5. The primary endpoint for AML subject cohorts was CRc (CR+CRi+CRp) rate at any time based on International Working Group (IWG) criteria (Cheson et al 2003). Adverse events (AEs) and LINE-1 DNA methylation pharmacodynamics were secondary endpoints for safety and biological activity.

Table 2 presents subject and disease characteristics of previously untreated elderly (≥65 years) subjects with AML enrolled in the study. Of 51 subjects enrolled in this cohort, 24 and 27 were randomized to dose levels of 60 mg/m^2/day and 90 mg/m^2/day, respectively. The deleterious effect of advanced age generally remains after accounting for other covariates (Appelbaum et al 2006). Subjects with advanced age ≥75 years represented 73% of subjects in the study. In addition 47%, 45%, and 35% had poor-risk cytogenetics, secondary AML, and ECOG PS 2, respectively. Subject characteristics were generally balanced between the 2 dose groups with few exceptions. Median age was 78 and 77 years; ECOG PS 2 was 46% and 26%; 58% and 59% were male; and 50% and 44% had poor-risk cytogenetics in the 60 and 90 mg/m^2/day dose groups, respectively. The proportion of subjects with poor PS and/or poor-risk cytogenetics was higher in the 60 mg/m^2 dose group. Overall, 31% of subjects had multiple criteria beyond advanced age that excluded them from candidacy for intensive induction chemotherapy. These criteria are established risk factors for more intensive induction chemotherapy for AML (Estey 2007).

Table 2: Characteristics of Previously Untreated Elderly (≥65 Years) Subjects with AML in the SGI-110 Phase 2 Study (Daily×5 Regimen)

Subject Characteristics	60 mg/m^2 (N=24)	90 mg/m^2 (N=27)	Total (N=51)
Median Age, years (range)	78 (62-92) [a]	77 (66-92)	77 (62-92) [a]
Age ≥75 years (n, %)	16 (67)	21 (78)	37 (73)
Gender (n, %)			
Men	14 (58)	16 (59)	30 (59)
Women	10 (42)	11 (41)	21 (41)
ECOG Performance Status (n, %)			
0	3 (13)	8 (30)	11 (22)
1	10 (42)	12 (44)	22 (43)
2	11 (46)	7 (26)	18 (35)
Median % BM Blast at Baseline (range)	40 (21-90) [b]	46 (13-94) [b]	40 (13-94) [b]
Secondary AML (n, %)	10 (42)	13 (48)	23 (45)
Poor-risk Cytogenetics [c] (n, %)	12 (50)	12 (44)	24 (47)
Major Organ Dysfunction (n, %)	1 (4)	2 (7)	3 (6)
Subjects with >1 criteria other than age (n, %)	8 (33)	8 (30)	16 (31)

[a] One 62-year-old subject had 2 comorbidities (secondary AML and poor-risk cytogenetics) and was allowed into the study on that basis.

[b] Four subjects had baseline BM differential blast counts of <20%: 2 of them had baseline peripheral blood (PB) blasts of 27% and 39%; the other 2 had BM pathology reports indicating either 40% blasts of total cellularity (Subject [redacted]) or 55% normoblasts (Subject [redacted]) and were thus diagnosed as AML (Listing BTA_Baseline 1 [15 April 2014] and BM pathology reports).

[c] Based on sponsor assessment.

Source: Table EOP2_DEMO 1 (14 May 2014) and EOP2_BASELINE 1 (7 May 2014)

The 60 and 90 mg/m^2 doses for the Daily×5 regimen showed similar activity (Table 3). CRc was observed in 13 subjects (8 CR+5 CRi; 54%) and 15 subjects (9 CR+6 CRi; 56%) for 60 and 90 mg/m^2 dose groups, respectively. CRc for both doses combined was achieved in 28 of 51 subjects (17 CR, 11 CRi, no CRp; 55%). CR rates were identical for the 2 doses at 33%.

Table 3: 60 vs 90 mg/m^2 (Daily×5 Regimen): Complete Response for Previously Untreated Elderly (≥65 Years) Subjects with AML (Phase 2)

	Response Rate (n, %)		
Response Category[a]	60 mg/m^2 (N=24)	90 mg/m^2 (N=27)	Total (N=51)
Complete response (CR)	8 (33) [95% CI: 16,55]	9 (33) [95% CI: 17,54]	17 (33) [95% CI: 21,48]
CR with incomplete blood count recovery (CRi)	5 (21)	6 (22)	11 (22)
CR with incomplete platelet recovery (CRp)	0	0	0
CRc rate (CR+CRi+CRp)	**13 (54)** [95% CI: 33,74]	**15 (56)** [95% CI: 35,75]	**28 (55)** [95% CI: 40,69]

[a] IWG 2003 AML Response Criteria (Cheson et al 2003).

Source: Table EOP2_RESP 3 (1 May 2014)

Table 4 shows that safety was generally comparable between 60 and 90 mg/m^2 SGI-110 doses in the Phase 2 study. Higher Grade ≥3 neutropenia was observed at the 90 mg/m^2 dose.

Table 4: 60 vs 90 mg/m^2 (Daily×5 Regimen): Previously Untreated Elderly Subjects with AML (Phase 2): Grade ≥3 AEs with Incidence ≥15%, Regardless of Relationship to SGI-110

	Number (%) of Subjects		
Adverse Event (AE) (MedDRA Preferred Term)	**60 mg/m^2 (N=24)**	**90 mg/m^2 (N=27)**	**Total (N=51)**
Any Grade ≥3 AE	22 (92)	25 (93)	47 (92)
Febrile neutropenia	13 (54)	13 (48)	26 (51)
Thrombocytopenia	12 (50)	10 (37)	22 (43)
Neutropenia	5 (21)	12 (44)	17 (33)
Anemia	7 (29)	6 (22)	13 (25)
Leukopenia	5 (21)	7 (26)	12 (24)
Pneumonia	5 (21)	5 (19)	10 (20)

Source: Table EOP2 AE_G3 6.3 (2 May 2014)

Treatment-related mortality in elderly patients on intensive induction remission therapy is usually high (on the order of 25% and up to 50%). Table 5 presents all-cause mortality in elderly subjects with AML from the Phase 2 study after SGI-110 treatment. The 30- and 60-day all-cause mortality rates were low (5.9% and 15.7%, respectively) when compared with intensive induction even though most intensive induction studies in the elderly reported only treatment-induced mortality rather than all-cause mortality (Estey 2007).

Table 5: 60 vs 90 mg/m^2 (Daily×5 Regimen): All-Cause Mortality in Previously Untreated Elderly Subjects with AML Treated with SGI-110 (Phase 2)

		Number (%) of Subjects	
Dose	**N**	**30-day Mortality**	**60-day Mortality**
All Previously Untreated AML	51	3 (5.9)	8 (15.7)
60 mg/m^2	24	2 (8.3)	4 (16.7)
90 mg/m^2	27	1 (3.7)	4 (14.8)

Source: EOP2_DEATH (26 Apr 2014 database cut-off date)

LINE-1 DNA methylation data before and after treatment were available in 49 subjects (96%). Average maximum LINE-1 demethylation was similar for the 60 mg/m^2 and 90 mg/m^2 dose groups (-19% for 60 mg/m^2 and -21% for 90 mg/m^2).

Based on a trend of improvement in response rate in relapsed/refractory AML with a 10-day regimen of SGI-110 (Section 1.3.2.2.2), a new cohort of 52 treatment-naïve elderly subjects with AML was treated with the 10-day regimen. Emerging preliminary data (study is still ongoing) suggest that this 10-day regimen in treatment-naïve elderly subjects is unlikely to be associated

with a significantly higher response rate than the Daily×5 regimen in this population and may be associated with higher toxicity.

1.3.2.2.2 Relapsed/Refractory AML

Subjects with relapsed/refractory AML were first randomly assigned to either 60 or 90 mg/m^2/day SGI-110 Daily×5. After completion of the SGI-110 Daily×5 cohort, an additional cohort of subjects with relapsed/refractory AML was treated with a 10-day regimen at the 60 mg/m^2 dose level (Days 1-5 and 8-12 every 28 days). After 2-4 cycles of the 10-day regimen, investigators were allowed to consolidate with the Daily×5 at 60 mg/m^2/day until progression. Table 6, Table 7, and Table 8 show clinical responses, common Grade ≥3 AEs, and all-cause mortality for subjects with relapsed/refractory AML. Data from the Daily×5 regimen are presented for both 60 and 90 mg/m^2 doses combined (there were no major differences between these doses; see Section 2.2.3.1) versus the 10-day regimen.

Table 6: Complete Response for Relapsed/Refractory Subjects with AML (Phase 2)

	Response Rate (n, %)	
Response Category[a]	**Daily×5 Regimen (60 or 90 mg/m^2) (N=50)**	**10-day Regimen (60 mg/m^2) (N=53)**
Complete response (CR) (%)	3[b] (6) [95% CI: 1,17]	10 (19) [95% CI: 9,32]
CR with incomplete blood count recovery (CRi)	4 (8)	2 (4)
CR with incomplete platelet recovery (CRp)	1 (2)	4 (8)
CRc rate (CR+CRi+CRp)	**8[c] (16)** [95% CI: 7,29]	**16 (30)** [95% CI: 18,44]

[a] IWG 2003 AML Response Criteria (Cheson et al 2003).
[b] 2 CR on 60 mg/m2 and 1 CR on 90 mg/m^2.
[c] 3 CRc on 60 mg/m^2 and 5 on 90 mg/m^2.
Source: Tables EOP2_RESP 2 (1 May 2014) and EOP2_RESP 1 (8 May 2014)

Table 7: Grade ≥3 AEs with Incidence ≥15%, Regardless of Relationship to SGI-110, in Relapsed/Refractory Subjects with AML (Phase 2)

AE (MedDRA Preferred Term)	**Daily×5 Regimen (60 or 90 mg/m^2) (N=50)**	**10-day Regimen (60 mg/m^2) (N=53)**
Any Grade ≥3 AE (n, %)	45 (90)	48 (91)
Febrile neutropenia (n, %)	30 (60)	31 (59)
Thrombocytopenia (n, %)	10 (20)	20 (38)
Neutropenia (n, %)	4 (8)	8 (15)
Anaemia (n, %)	9 (18)	19 (36)
Pneumonia (n, %)	12 (24)	15 (28)

Source: Table EOP2 AE_G3 6.3 (2 May 2014)

Table 8: All-Cause Mortality in Relapsed/Refractory Subjects with AML (Phase 2)

		Mortality	
Dose	**N**	**30-day (%)**	**60-day (%)**
Daily×5 Regimen (60 or 90 mg/m^2)	50	3 (6.0)	6 (12.0)
10-day Regimen (60 mg/m^2)	53	1 (1.9)	6 (11.3)

Source: EOP2_DEATH (26 Apr 2014 database cut-off date)

SGI-110 showed clinical activity, but complete responses with SGI-110 in relapsed/refractory AML (CRc rate of 16% and 30% for the Daily×5 and 10-day regimens, respectively; Table 6) were lower than what was observed in treatment-naïve elderly subjects with AML (CRc rate of 55% for the Daily×5 regimen; Table 3). In relapsed/refractory AML, the 10-day regimen showed a trend of higher response rate and higher Grade ≥3 myelosuppression, with no difference in early all-cause mortality.

1.4 Summary of Data for Treatment Choice (TC)

Treatment choice (TC) will be compared with SGI-110 therapy in this study because no standard therapy exists for patients with previously untreated AML who are not considered candidates for intensive remission induction therapy. Available local TCs will depend on which TCs are approved locally. TC includes any of the following:

- 20 mg cytarabine given SC twice daily (BID) on Days 1-10 every 28 days.
- 20 mg/m^2 decitabine given intravenously (IV) daily on Days 1-5 every 28 days.
- 75 mg/m^2 azacitidine given IV or SC daily on Days 1-7 every 28 days.

As detailed in Section 1.2, each of these choices is supported by data from randomized clinical multicenter trials (Burnett et al 2007; Fenaux et al 2010; Kantarjian, Thomas et al 2012; Dombret et al. 2014). They are used as standard of care and/or recommended by the NCCN, European Leukemia Net, and European Society for Medical Oncology. There have been no direct comparisons among them, and regional treatment standards vary.

1.5 Potential Risks and Benefits to Human Subjects

Commonly observed AEs in Study SGI-110-01 in subjects with AML or MDS include injection site AEs, febrile neutropenia, thrombocytopenia, anemia, diarrhea, fatigue, and nausea. All these AEs are expected risks of SGI-110 in this Phase 3 trial in AML. These and additional risks in humans are described further in Section 8.0, Risks/Precautions. For more detailed information, please refer to the IB for SGI-110.

Potential benefits of SGI-110 include symptom improvement, achieving leukemia disease remission, delayed disease progression, delayed need for subsequent anticancer therapy, and prolongation of survival.

For risks and benefits of TC therapies, refer to the latest locally-approved Prescribing Information for each therapy (USA examples: Cytarabine 2008, Dacogen 2010, Vidaza 2014).

Risk-benefit considerations favor performance of this trial. This study population has limited therapeutic options, and available therapies are of limited utility. SGI-110 has demonstrated clinical activity and the potential to generate improved benefit over TC in AML.

2.0 RATIONALE

2.1 Rationale for the Study

Rationale for this study comes from SGI-110's molecular structure, PK, pharmacodynamic (PD), and clinical data.

SGI-110's dinucleotide structure protects the active decitabine moiety from inactivation by cytidine deaminase (CDA). Human PK data confirms that gradual in vivo dinucleotide cleavage increases decitabine exposure time and effective half-life relative to decitabine IV infusion. Prolonged exposure time is predicted to increase efficacy because decitabine activity is dependent on its incorporation into DNA during DNA synthesis, ie, S-phase of the cell cycle (Griffiths, Choy et al 2013; Karahoca and Momparler 2013). Prolonged exposure results in more cancer cells susceptible to decitabine activity as they enter into S-phase. Also, a lower decitabine C_{max} after SGI-110 relative to decitabine IV infusion might improve safety for toxicities associated with peak decitabine concentrations.

During the FIH Phase 1 SGI-110-01 Dose Escalation, potent DNA demethylation, CR and other clinical responses were observed in heavily pretreated subjects with AML and MDS, including those previously treated with other existing HMAs (decitabine and azacitidine).

In the Phase 2 SGI-110-01 Dose Expansion, 51 elderly subjects with AML who had other poor prognostic features and were not eligible for intensive chemotherapy received SGI-110. The observed CR rate of 33% and CRc rate of 55% exceeded those observed for currently available therapies in randomized, multicenter studies (see Table 9). Due to heterogeneity of subjects in single-center, nonrandomized studies with the consequent risk of selection bias, we selected recently published, randomized, multicenter studies of agents commonly used as standard of care for elderly patients with AML. Data in Table 9 indicate that SGI-110 may improve efficacy over other therapies for this AML patient population.

Table 9: SGI-110 Response Compared with Other Therapies for Previously Untreated Elderly Subjects with AML

	Number (%) Subjects				
	Phase 2	Kantarjian, Thomas et al. 2012		Dombret et al 2014	Burnett et al 2007
Response	SGI-110 (N=51)	Decitabine IV (N=242)	LDAC (N=215)	Azacitidine (N=241)	LDAC (N=102)
CR	17 (33) [21~48][a]	38 (16)	17 (8)	48 (20)	18 (18)
CRc	28 (55) [40~69][a]	67 (28)	24 (11)	67 (28)	Unknown

[a] 95% CI based on a binomial distribution.

Source: SGI-110 Phase 2: Table EOP2_RESP 3 (1 May 2014)

Safety as assessed by early 30- and 60-day all-cause mortality rates, as well as Grade ≥3 toxicities, are comparable to those of TC therapies except for a higher incidence of febrile neutropenia on SGI-110 (Table 10).

Table 10: SGI-110 Safety Compared with Other Therapies for Previously Untreated Elderly Subjects with AML

Common Grade ≥3 AEs and All-Cause Mortality	% Subjects				
	Phase 2	Kantarjian, Thomas et al. 2012		Dombret et al 2014	Burnett et al 2007
	SGI-110 (N=51)	Decitabine IV (N=238)[a]	LDAC (N=208)[a]	Azacitidine (N=241)	LDAC (N=102)[a]
Febrile Neutropenia	51%	32%	25%	28%	Unknown
Thrombocytopenia	43%	40%	35%	24%	Unknown
Neutropenia	33%	32%	20%	26%	Unknown
Anemia	25%	34%	27%	16%	Unknown
30-day mortality	5.9%	9%	8%	6.6%	26%
60-day mortality	15.7%	19.7%	23%	16.2%	Unknown

[a] Number of subjects smaller than in Table 9, reflecting subjects who actually received treatment.

2.2 Rationale for SGI-110 Dose and Regimen

The dose and regimen of SGI-110 proposed for this Phase 3 study is based on dose-response data evaluated from all PK, PD, efficacy, and safety information available from Phase 1 and 2 investigations.

2.2.1 PK Dose Assessment

PK profiles from 85 subjects who received doses ranging from 3 to 125 mg/m^2 showed that the dose levels of 60 and 90 mg/m^2 bracket the AUC expected from active metabolite decitabine at the FDA-approved dose of 20 mg/m^2 of decitabine IV. Decitabine AUCs resulting from

treatment with SGI-110 at dose levels of 60 and 90 mg/m^2 are 78% and 130%, respectively, of the AUC of decitabine IV (20 mg/m^2) (Table 11).

Table 11: Dose Selection PK Data: Decitabine Exposure (Mean ± SD) after SGI-110 Treatment (36–125 mg/m^2/day on Days 1-5)

Dose (N)	C_{max} (ng/mL)	C_{max} fraction of IV[a]	AUC_{last} (ng*hr/mL)	AUC fraction of IV[a]
36 mg/m^2 (12)	16.5 ± 8.1	0.11	56.7 ± 18.7	0.49
60 mg/m^2 (20)	27.4 ± 21.5	0.19	89.2 ± 52.9	0.78
90 mg/m^2 (14)	41.4 ± 20.4	0.28	149 ± 54.7	1.30
125 mg/m^2 (18)	64.2 ± 24.4	0.44	239 ± 68.0	2.08

[a] Relative to values from decitabine IV (1-hr, 20 mg/m^2) C_{max} 147 ng/mL; AUC_{0-t} 115 ng*hr/mL.

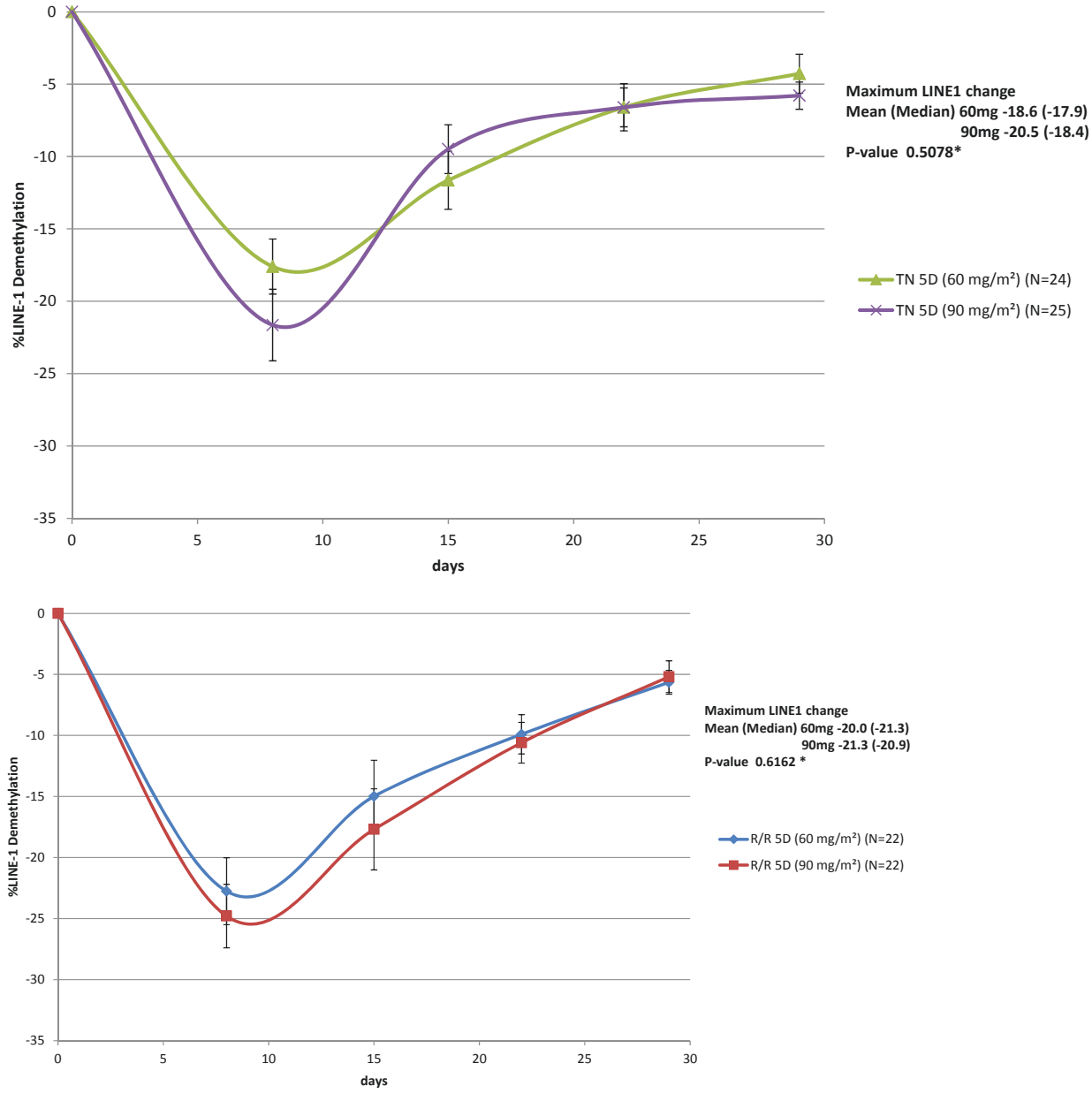
Source: SGI-110 IB

2.2.2 PD Dose Assessment: LINE-1 DNA Methylation

In the SGI-110-01 Dose Escalation study, we assessed weekly LINE-1 DNA methylation in Cycle 1 as a surrogate of global DNA methylation and biological activity in 65 subjects on either the Daily×5 schedule (35 subjects) or the Once Weekly schedule (30 subjects) over a range of 8 dose levels: 3, 9, 18, 36, 60, 90, or 125 mg/m^2/day). Data showed superior dose-dependent-biological activity of the Daily×5 schedule over the Once Weekly schedule (Figure 1). Of 35 subjects on the Daily×5 schedule, dose-dependent increase in demethylation occurred up to 60 mg/m^2/day with no further demethylation at higher doses. These data support an increase in DNA demethylation up to 60 mg/m^2/day on Days 1-5 (Figure 1).

Maximum demethylation at 60 mg/m^2/day for 5 days met the prospectively defined BED endpoint in the Phase 1 study. This observation was later confirmed in the Phase 2 randomization between 60 and 90 mg/m^2/day on Days 1-5, where in 93 AML patients (49 with treatment-naïve elderly AML and 44 with relapsed/refractory AML), there was no significant difference in LINE-1 demethylation between 60 and 90 mg/m^2 Daily×5 (Figure 2).

Figure 2: Dose Selection PD (60 vs 90 mg/m^2/day, 5-Day Regimen SGI-110): Mean LINE-1 Demethylation in Treatment-naïve Subjects (top) and Relapsed/Refractory Subjects with AML (bottom)



* Overall group effect from a repeated measures mixed model analysis.

TN=treatment-naïve; R/R=relapsed/refractory; 5D=5-day regimen (Daily×5)

Source: Yee et al 2014 (top), Kantarjian et al 2013 (bottom)

2.2.3 Clinical Efficacy and Safety SGI-110 Dose-response

2.2.3.1 Daily×5 Regimen in AML

We conducted a randomized, dose-response, Phase 2 study in 101 subjects with AML (51 treatment-naïve elderly and 50 relapsed/refractory) that compared therapy with 60 versus 90 mg/m^2/day SGI-110 on Days 1-5 (see also Section 1.3.2.2). While the CR rate differed between the 2 different AML subject populations, efficacy of the 2 doses was remarkably similar (Table 12). Compared with the 60 mg/m^2/day dose, the 90 mg/m^2/day dose showed increased Grade ≥3 febrile neutropenia and pneumonia in relapsed/refractory AML subjects, and increased Grade ≥3 neutropenia in treatment-naïve AML subjects (Table 13). Overall, the incidence of AEs Grade ≥3 was similar between the doses. Mortality rates were low overall at both dose levels (Table 14). In conclusion, with the Daily×5 regimen, the dose of 60 mg/m^2/day is selected based on similar efficacy to the higher dose of 90 mg/m^2/day and potential for lower toxicity.

Table 12: Dose Selection (60 vs 90 mg/m^2/day, 5-day regimen): Complete Response Summary in Subjects with AML (Phase 2)

	Response Rate (Number [%] of Subjects)					
	Relapsed/Refractory		Treatment-naïve Elderly		All	
Response Category[a]	60 mg/m^2 (N=24)	90 mg/m^2 (N=26)	60 mg/m^2 (N=24)	90 mg/m^2 (N=27)	60 mg/m^2 (N=48)	90 mg/m^2 (N=53)
CR	2 (8)	1 (4)	8 (33)	9 (33)	10 (21)	10 (19)
CRp	0	1 (4)	0	0	0	1 (2)
CRi	1 (4)	3 (12)	5 (21)	6 (22)	6 (13)	9 (17)
CRc (CR+CRp+CRi)	3 (13)	5 (19)	13 (54)	15 (56)	16 (33)	20 (38)

[a] IWG 2003 AML Response Criteria (Cheson et al. 2003).
Source: Table EOP2_RESP1 (8 May 2014), Table EOP2_RESP3 (1 May 2014) (Database 26 April 2014)

Table 13: Dose Selection (60 vs. 90 mg/m^2/day, 5-day regimen): Grade ≥3 AEs with Incidence ≥15%, Regardless of Relationship to SGI-110 in Subjects with AML (Phase 2)

	Number (%) of Subjects					
	Relapsed/Refractory		Treatment-naïve Elderly		All	
Event	60 mg/m^2 (N=24)	90 mg/m^2 (N=26)	60 mg/m^2 (N=24)	90 mg/m^2 (N=27)	60 mg/m^2 (N=48)	90 mg/m^2 (N=53)
Any Grade ≥3 AE	20 (83)	25 (96)	22 (92)	25 (93)	42 (88)	50 (94)
Febrile neutropenia	12 (50)	18 (69)	13 (54)	13 (48)	25 (52)	31 (58)
Thrombocytopenia	6 (25)	4 (15)	12 (50)	10 (37)	18 (38)	14 (26)
Neutropenia	2 (8)	2 (8)	5 (21)	12 (44)	7 (15)	14 (26)
Leukopenia	3 (13)	2 (12)	5 (21)	7 (26)	8 (17)	9 (17)
Anemia	5 (21)	4 (15)	7 (29)	6 (22)	12 (25)	10 (19)
Pneumonia	4 (17)	8 (31)	5 (21)	5 (19)	9 (19)	13 (25)
Hypokalemia	5 (21)	3 (12)	2 (8)	5 (19)	7 (15)	8 (15)

Source: EOP2_AE_G3 6.1 (2 May 2014; from database 26 April 2014)

Table 14: Dose Selection (60 vs 90 mg/m^2/day, 5-day regimen): All-Cause Early Mortality in Subjects with AML (Phase 2)

	Number (%) of Subjects					
	Relapsed/Refractory		Treatment-naïve Elderly		All	
Mortality	60 mg/m^2 (N=24)	90 mg/m^2 (N=26)	60 mg/m^2 (N=24)	90 mg/m^2 (N=27)	60 mg/m^2 (N=48)	90 mg/m^2 (N=53)
30-day	2 (8.3)	1 (3.8)	2 (8.3)	1 (3.7)	4 (8.3)	2 (3.8)
60-day	4 (16.7)	2 (7.7)	4 (16.7)	4 (14.8)	8 (16.7)	6 (11.3)

Source: EOP2_DEATH (database date 26 April 2014)

2.2.3.2 10-day Regimen in AML

The results of the 10-day regimen using 60 mg/m^2/day in relapsed/refractory AML are presented in Section 1.3.2.2.2 (Table 6, Table 7, and Table 8). While the 10-day regimen showed a trend toward improved response rate in relapsed/refractory AML, it also resulted in more myelosuppression. Study of treatment-naïve elderly AML subjects with the 10-day regimen of SGI-110 is ongoing, but emerging preliminary data suggest that response rates are unlikely to be significantly higher than those observed with the Daily×5 regimen (CRc of 55%) and that the toxicity of the 10-day regimen in these older subjects could be more pronounced. The results of the 10-day regimen in these subjects after at least 3 months follow-up showed a CRc and CR of only 44% and 25%, respectively (compared with 55% and 33%, respectively, for the 5-day regimen) with higher 60-day all-cause mortality of 19.2% (compared with 15.7% for the 5-day regimen). In addition, the safety database at the time of analysis shows drug-related serious adverse events (SAEs) of 42% (compared to 16% for the 5-day regimen). Based on absence of higher response rate and the trend of higher early mortality and drug-related SAEs with the 10-day regimen in elderly subjects who are not candidates for intensive chemotherapy, the 5-day regimen is selected as the one associated with the best benefit-risk in this population. Higher response rates and favorable safety for the SGI-110 Daily×5 regimen compared with other treatments have already been observed in the proposed study population (Section 2.1, Table 9), so it is reasonable to propose this regimen in the phase 3 study.

2.2.4 Dose Selection Conclusion from Phase 1 and 2 Study

The SGI-110 Daily×5 regimen at 60 mg/m^2/day provides the best benefit-risk ratio for the treatment of treatment-naïve elderly AML subjects based on available data. This regimen is supported by PK, PD, efficacy, and safety data from Study SGI-110-01. Results were similar but not demonstrably better at the 90 mg/m^2 dose level, and based on potential dose-limiting myelosuppression, the 60 mg/m^2 dose level is likely to be better tolerated over time.

3.0 STUDY OBJECTIVES

3.1 Primary Objective

To assess and compare efficacy (CR rate and OS) between SGI-110 and TC in adults with previously untreated AML who are not considered candidates for intensive remission induction chemotherapy.

3.2 Secondary Objectives

To assess and compare effects of SGI-110 and TC in adults with previously untreated AML who are not considered candidates for intensive remission induction chemotherapy with respect to the following variables:

- CRc (CR+CRi+CRp) rate.
- Number of days alive and out of the hospital (NDAOH).
- Progression-free survival (PFS).
- Transfusion needs.
- Health-related quality of life (QOL).
- Duration of CR.
- Safety.

3.3 Exploratory Objectives

- [redacted]
- [redacted]

4.0 INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is a phase 3, multicenter, randomized, open-label study of SGI-110 versus TC. Blinded central reading of marrow and disease response will be performed. Subjects will be adults with previously untreated AML who are unfit to receive and not candidates for intensive remission induction chemotherapy.

Approximately 800 subjects from approximately 100-160 study centers will be randomly assigned (1:1) to 1 of 2 groups:

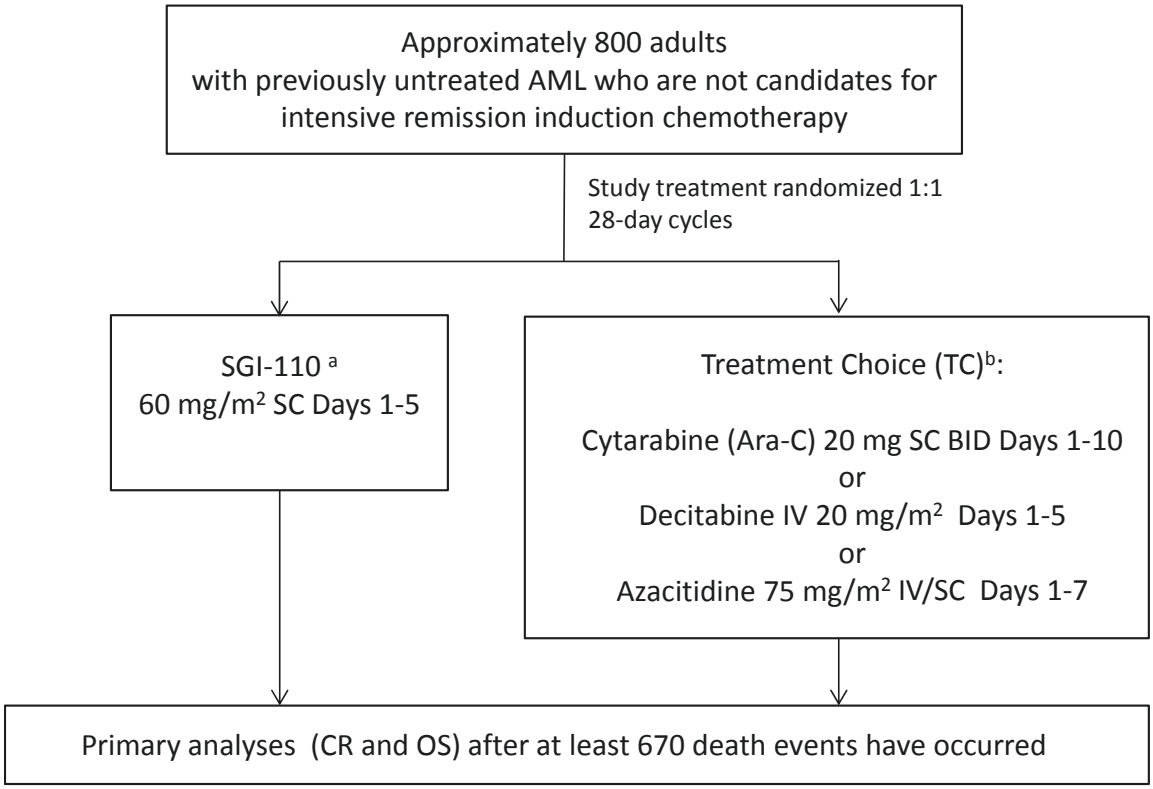
- SGI-110: 60 mg/m^2 SGI-110 given SC daily for 5 days (Days 1-5, Daily×5) in 28-day cycles.
- TC: subjects will be assigned (before randomization) by the investigator to 1 of the following treatment regimens:

- 20 mg cytarabine given SC BID on Days 1-10 every 28 days.
- 20 mg/m^2 decitabine given IV daily on Days 1-5 every 28 days.
- 75 mg/m^2 azacitidine given IV or SC daily on Days 1-7 every 28 days.

Data will be reviewed by an independent Data Monitoring Committee (DMC) at regular intervals primarily to evaluate safety during study conduct. Refer to Section 4.4.

The co-primary endpoints will be CR rate and OS. If either of the co-primary efficacy endpoints reaches statistical significance in favor of SGI-110 at either the interim analysis (OS only) or final analysis (CR and OS), then the study will be considered positive in efficacy. Randomization and analyses will be stratified by age, ECOG performance status (see Appendix 1), study center region, and secondary AML or poor-risk cytogenetics (see Appendix 2).

Figure 3: Study Schema



[a] Treatment with SGI-110 should continue for at least 6 cycles in the absence of unacceptable toxicity or AML progression requiring alternative therapy. Beyond 6 cycles, treatment should continue as long as the subject continues to benefit based on investigator judgment.

[b] TC will be determined before randomization and treatment with the regimens described (Section 7.2) should be used. Other treatment parameters should be applied according to institutional standard practice and approved local prescribing information.

4.2 Discussion of Study Design

This trial compares SGI-110 and TC for treatment of subjects with AML who are not considered candidates for intensive remission induction chemotherapy at the time of enrollment. While the 7+3 intensive chemotherapy for remission induction with potential for hematopoietic cell transplant (HCT) has been an established standard of care for decades in patients who are fit to receive this intensive treatment, there is no standard of care or universally approved therapies for treatment of AML patients who are not candidates for standard intensive remission induction chemotherapy. For these patients, goals of therapy are to prolong and improve quality of life by inducing complete remission for as long as possible, as well as to avoid treatment-induced early mortality.

Eligibility for this trial is based on precedented criteria of unsuitability for intensive remission induction chemotherapy (Ferrara et al 2013; Kantarjian et al 2006; Kantarjian et al 2010) and other randomized trials in a similar patient population (Burnett et al 2007; Kantarjian, Thomas et al 2012; Dombret et al 2014). The co-primary endpoints for this trial are CR rate and OS.

FDA has accepted durable CR in hematological malignancies as an established surrogate for clinical benefit because patients who achieve durable CR have been shown to survive longer than those who do not (Appelbaum et al 2007). Numerous studies have demonstrated that subjects achieving CR survive longer than subjects not achieving CR (Sievers et al 2001; Larson et al 2005; de Greef et al 2005; Kantarjian et al 2003). FDA has also granted regular approval for treatment of hematologic malignancies on the basis of durable CR. In these settings, durable CRs were considered an established surrogate for a better life and possibly a longer life (Johnson et al 2003).

The trial includes a co-primary endpoint of OS to confirm no decrement in survival from severe toxicity. Secondary endpoints include CRc (CR+CRi+CRp) rate, NDAOH, PFS, number of transfusions, health-related QOL, duration of CR, and safety.

TC, the control therapy for this study, includes treatments listed in Section 4.1. These therapies have not been compared directly, and regional treatment standards vary. Hence, all of these are allowed. All TC comparators are approved regimens for these agents mainly for other indications but have shown evidence of efficacy and safety from randomized trials in AML patient populations similar to the study population (Burnett et al 2007; Kantarjian, Thomas et al 2012; Dombret et al 2014). Each country will use the TC option(s) that are locally approved.

This study is open-label. It is difficult to conduct such a trial in a blinded fashion because of the significant differences in the treatment schedules and the multiple treatment choices. The risk of observer bias can be controlled effectively by a central pathologist and a central response reviewer, who will be blinded to treatment assignment and independent (Section 6.2). OS endpoint is not prone to observer bias.

4.3 Study Endpoints

4.3.1 Co-primary Endpoints

- CR rate based on modified IWG 2003 AML Response Criteria.
- OS, defined as the number of days from randomization to death.

4.3.2 Secondary Endpoints

- CRc (CR+CRi+CRp) rate.
- NDAOH.
- PFS, defined as the number of days from randomization to disease progression or death, whichever occurs first.
- Number of red blood cell (RBC) or platelet transfusions (units) over the duration of the study treatment.
- Health-related QOL by EQ-5D (consisting of the EQ-5D-5L descriptive system and the EQ Visual Analogue Scale [EQ VAS]).
- Duration of CR, defined as defined as the time from first CR to time of relapse.
- Incidence and severity of AEs.
- 30- and 60-day all-cause mortality.

4.4 Data Monitoring Committee (DMC)

An independent DMC will be established for this study. The DMC is an independent multidisciplinary group consisting of hematologic oncology experts and 1 biostatistician who, collectively, have experience in the treatment of subjects with AML and in the conduct and monitoring of clinical studies. The DMC will independently analyze accumulating data and make recommendations to the sponsor and the Study Steering Committee (SSC), as needed, to modify or discontinue the trial. DMC reviews will occur approximately each 6 months and as needed following study initiation until the final analyses. The DMC will also conduct independent interim analysis of OS as detailed in Section 11.0 and in a separate DMC Charter. The DMC will not stop the trial early based on the observed difference in CR.

Details of DMC membership, responsibilities, meeting frequency and format, review materials, and communication plan will also be described in the DMC Charter.

4.5 Study Steering Committee (SSC)

An SSC composed of the lead investigators in the different study center regions, and sponsor representatives, will be formed to review study conduct at regular intervals, address any issues or recommend changes during the study conduct, and advise the sponsor on implementation of any DMC recommendations. SSC operational details will be described in a separate document.

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Number of Subjects and Centers

Approximately 800 subjects will be enrolled in this study at approximately 100-160 study centers.

5.2 Inclusion Criteria

To be eligible for the study, subjects must fulfill all of the following inclusion criteria:

1. Able to understand and comply with the study procedures, understand the risks involved in the study, and provide written informed consent before any study-specific procedure.
2. Cytologically or histologically confirmed diagnosis of AML (except M3 acute promyelocytic leukemia) according to the 2008 WHO classification (with BM or PB blast counts ≥20%).
3. Performance status (ECOG) of 0-3.
4. Adults with previously untreated AML except for hydroxyurea or corticosteroids. Prior hydroxyurea or lenalidomide treatment for MDS is allowed.
5. Unfit to receive or not considered candidates for intensive remission induction chemotherapy at time of enrollment based on EITHER:
   a. ≥75 years of age
      OR
   b. <75 years of age with at least 1 of the following:
      i. Poor performance status (ECOG) score of 2-3.
      ii. Clinically significant heart or lung comorbidities, as reflected by at least 1 of:
         1) LVEF ≤50%.
         2) DLCO ≤65% of expected.
         3) FEV_1 ≤65% of expected.
         4) Chronic stable angina or congestive heart failure controlled with medication.
      iii. Liver transaminases >3 × upper limit of normal (ULN).
      iv. Other contraindication(s) to anthracycline therapy (must be documented).
      v. Other comorbidity the investigator judges incompatible with intensive remission induction chemotherapy which must be documented and approved by the study medical monitor before randomization.
6. Creatinine clearance as estimated by the Cockroft-Gault (C-G) or other medically acceptable formulas ≥30 mL/min.

7. Women of child-bearing potential must not be pregnant or breastfeeding and must have a negative pregnancy test at screening. Women of child-bearing potential and men with female partners of child-bearing potential must agree to practice 2 highly effective contraceptive measures during the study and for at least 3 months after completing treatment and must agree not to become pregnant or father a child while receiving treatment with SGI-110 and for at least 3 months after completing treatment. Contraceptive measures which may be considered highly effective comprise combined hormonal contraception (oral, vaginal, or transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, sexual abstinence, and surgically successful vasectomy. Abstinence is acceptable only if it is consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of birth control.

5.3 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. Candidate for intensive remission induction chemotherapy at the time of enrollment.
2. Candidate for best supportive care only, ie, not a candidate for any active therapy with the TC comparators.
3. Known extramedullary central nervous system (CNS) AML.
4. Second malignancy currently requiring active therapy except breast or prostate cancer stable on or responding to endocrine therapy.
5. Prior treatment with decitabine or azacitidine.
6. Hypersensitivity to decitabine, azacitidine, cytarabine, SGI-110, or any of their excipients.
7. Treated with any investigational drug within 2 weeks of first dose of study treatment.
8. Total serum bilirubin >2.5 × ULN, except for subjects with Gilbert's Syndrome for whom direct bilirubin is <2.5 × ULN, or liver cirrhosis or chronic liver disease Childs-Pugh B or C.
9. Known active human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infection. Inactive hepatitis carrier status or low viral hepatitis titer on antivirals is allowed.
10. Known significant mental illness or other condition such as active alcohol or other substance abuse or addiction that, in the opinion of the investigator, predisposes the subject to high risk of noncompliance with the protocol.
11. Refractory congestive heart failure unresponsive to medical treatment; active infection resistant to all antibiotics; or advanced pulmonary disease requiring >2 liters per minute (LPM) oxygen.

5.4 Treatment Discontinuation and Withdrawal of Subjects

Subjects who discontinue study treatment will be followed up for important study data, as described below, unless they withdraw consent from further follow-up.

5.4.1 Discontinuation from Study Treatment

Subjects who discontinue study treatment will still continue study follow-up procedures. Investigators are encouraged to assess all subjects according to the study protocol after discontinuation from study treatment.

- Investigators can discontinue subjects from study treatment in case of unacceptable toxicity, noncompliance, disease progression requiring alternative therapy, if the investigator determines it is in the subject's best interest, or if the subject becomes pregnant.
- Astex Pharmaceuticals may require that a subject is discontinued from treatment for safety reasons or for noncompliance.

In all cases, the reason(s) for discontinuation from study treatment must be recorded in the source document and on the relevant page of the subject's electronic case report form (eCRF).

It is important to obtain protocol-specified follow-up information on any subject discontinued from study treatment. Section 10.0 describes follow-up for AEs. At minimum, subjects should be followed up for safety until 30 days after the last dose of study treatment (ie, discontinuation of treatment in the study) (see Section 10.2).

5.4.2 Withdrawal from the Study

Subjects may withdraw consent for the study at any time, or subjects may be lost to follow-up. It is important to obtain follow-up information, according to standard medical practice, on any subject withdrawn prematurely from the study. Every effort must be made to undertake at least standard assessments that are critical for efficacy or safety evaluation, such as disease progression (if the subject did not withdraw because of disease progression), subsequent anti-leukemia treatment, survival information, and safety data.

The investigator must also ensure the subject understands that his or her medical records will continue to be available for the follow-up period as described in the approved informed consent form (ICF) for the entire study period.

5.4.3 Replacement of Subjects

Subjects will not be replaced in this study.

6.0 ENROLLMENT, RANDOMIZATION, AND BLINDING PROCEDURES

Subjects will be screened at each study center for assessment of eligibility for the study. Each subject will be assigned a unique number (subject number) which will comprise the center number and the assigned subject number within the center. This number will be used to identify the subject throughout the study.

6.1 Randomization

Eligible subjects will be randomly assigned to study treatment. Treatment assignments for the individual subjects will be determined through a computer generated randomization scheme and accessed through an interactive response system. Instructions for access and use of the interactive response system for randomization will be provided to participating study centers separately. Randomization will be 1:1 between SGI-110 and TC groups, and will be stratified by age (<75 or ≥75 years), ECOG performance status (0-1 or 2-3; see Appendix 1 for the ECOG criteria), study center region (North America, Europe, rest of world [ROW]), and secondary AML (secondary to MDS or other antecedent hematologic disorder) or poor-risk cytogenetics (either, neither; see Appendix 2). Selection of 1 of the TCs must be made prior to the randomization of each subject. Subjects should receive study treatment as soon as possible after randomization (maximum of 1 week between randomization and treatment).

6.2 Blinding

The sponsor, investigators and study subjects are not blinded in this study. However, to minimize the potential bias associated with assessment of treatment outcome, response will be determined by a blinded independent central response reviewer, based on assessment by a blinded independent central pathologist. Refer to Section 11.6. The specific process used for handling test samples and reports will be described separately.

7.0 STUDY TREATMENTS

SGI-110 is the Investigational Medicinal Product (IMP) (Section 7.1), and Treatment Choice (TC) is the active comparator (Section 7.2).

7.1 Investigational Medicinal Product (IMP): SGI-110

SGI-110 chemical name: Sodium (*2R,3S,5R*)-5-(4-amino-2-oxo-1,3,5-triazin-1(2*H*)-yl)-2 (hydroxymethyl) tetrahydrofuran-3-yl ((*2R,3S,5R*)-5-(2-amino-6-oxo-1*H*-purin-9(6*H*)-yl)-3-hydroxytetrahydrofuran-2-yl)methyl phosphate

7.1.1 IMP Information

SGI-110 product is supplied in a two-vial configuration.

SGI-110 for Injection, 100 mg is a glass vial containing lyophilized SGI-110 drug powder for reconstitution and SC injection using the custom diluent supplied in a separate vial. Each vial is stoppered and sealed with a flip-off cap.

SGI-110 Diluent for Reconstitution, 3 mL is a glass vial with 3 mL of custom diluent. Each vial is stoppered and sealed with a flip-off cap. The diluent comprises 3 commonly used excipients, propylene glycol, glycerin, and ethanol, that are generally recognized as safe.

Store the SGI-110 for Injection, 100 mg vial, in the original packaging, refrigerated (2°C to 8°C) in a secure, locked facility accessible only to authorized study personnel until use. Store SGI-110 Diluent for Reconstitution, 3 mL at 2°C to 30°C in the upright position until use. Both vials are preservative free and for single use only. The sponsor will retest the SGI-110 at regular intervals, according to ICH guidelines, and if warranted, the expiration date will be extended and documented accordingly.

The sponsor recommends following Occupational Safety and Health Administration (OSHA) Guidelines for handling cytotoxic drugs outlined in Yodaiken and Bennett 1986 or similar institutional or country-specific guidelines. Preparation should occur according to institutional practice. For skin contact or spillage, refer to the material safety data sheet (MSDS) for treatment options.

Reconstituted drug product is intended for SC administration at a recommended concentration of 100 mg/mL.

7.1.2 SGI-110 Regimens and Administration

The SGI-110 regimen for this study is 60 mg/m^2 given Daily×5 (Days 1-5 in a 28-day cycle) for at least 6 cycles in the absence of unacceptable toxicity or AML progression for which the investigator intends to offer an alternative therapy. Beyond 6 cycles, treatment should continue as long as the subject continues to benefit based on investigator judgment. In the ongoing phase 2 dose expansion study (Section 1.3.2.2), some subjects responded late to treatment: of 51 treatment-naïve elderly AML subjects, 2 subjects responded, and another 2 subjects improved their response status from CRi or CRp to CR, after more than 6 treatment cycles with SGI-110.

Administer SGI-110 by SC injection, preferably in the abdominal area, upper thigh, or arm. The total amount (in mg) of SGI-110 to be administered is determined by body surface area (BSA). In calculating BSA, use actual heights and weights. Do not adjust to "ideal" body weight. The institutional standard for calculating BSA is acceptable.

Take care to avoid intradermal injection, as this may result in injection site pain (see Section 8.0).

Additional guidelines regarding SC injection will be detailed in the study procedures manual.

Investigators are prohibited from supplying SGI-110 to any subject not enrolled in this study or to any physicians or scientists except those designated as sub-investigators. The investigator must ensure that subjects receive SGI-110 only from personnel who fully understand the procedures for administering the study treatment.

7.2 Treatment Choice (TC) Active Comparator

TC will be one of the following treatment regimens (dose, schedule, and administration route) based on regimens approved by regulatory agencies, on published randomized studies, and on recommendations by the NCCN, European Leukemia Net, and European Society for Medical Oncology:

- 20 mg cytarabine given SC twice daily (BID) on Days 1-10 every 28 days.
- 20 mg/m^2 decitabine given IV daily on Days 1-5 every 28 days.
- 75 mg/m^2 azacitidine given IV or SC daily on Days 1-7 every 28 days.

Other use and treatment parameters of TC drugs (such as duration of treatment and dose adjustment guidelines) should follow locally approved prescribing information and institutional standard practice.

Examples of locally approved prescribing information are the following: Cytarabine 2008, Dacogen 2010, Vidaza 2014 (USA); and Cytarabine 20mg/ml 2014, Dacogen 50 mg powder for concentrate for solution for infusion 2014, Vidaza 25 mg/ml powder for suspension for injection 2014 (UK).

If a subject must discontinue TC study treatment, alternative therapy should be determined by the physician or institutional standard practice. Subjects randomly assigned to TC study treatment will not be allowed to receive SGI-110 as alternative therapy.

7.3 Guidelines for Adjusting or Withholding Study Treatment

7.3.1 Guidelines for SGI-110

SGI-110 study therapy is intended to be administered for a minimum of 6 total cycles.

It is recommended that the initial dose of SGI-110 is given on schedule (every 28 days) for the first 2 cycles without dose modification regardless of blood counts recovery to ensure initial dose intensity. Timing of cycle initiation and dose level of SGI-110 starting Cycle 3 will be guided by peripheral blood (PB) blast and neutrophil/platelet counts after the prior cycle, as indicated in Table 15, which describes dose modification based on Day 29 or later PB counts.

Table 15: SGI-110 Dosing Adjustment Guideline Based on End of Cycle ≥2 (C≥2, Day 29 or Later) Peripheral Blood Blasts and Counts

Neutrophils Platelets Threshold	Peripheral Blood (PB) Blasts		
	Presence of leukemic blasts	No leukemic blasts and recovery within <2 weeks	No leukemic blasts and recovery after >2 weeks
Neutrophils <1000/μL or Platelets <50,000/μL	Administer full dose on schedule.	Delay SGI-110 until counts >threshold, then administer full dose.	Delay study drug until counts >threshold, then reduce 1 dose level.
Neutrophils ≥1000/μL and Platelets ≥50,000/μL	Administer full dose on schedule.	Administer full dose on schedule.	Delay study drug until counts >threshold, then reduce 1 dose level.

For subjects with CRi or CRp for at least 2 cycles, SGI-110 treatment should be reduced 1 dose level at a time in each subsequent cycle until normal counts recover to levels of full CR (neutrophils ≥1000/μL and platelets ≥100,000/μL). The highest dose level that achieves normal counts recovery should be kept for subsequent cycles. Recommended reduced SGI-110 dose levels should be from 60 mg/m^2/day to 45 mg/m^2/day, then to 30 mg/m^2/day, and then to 15 mg/m^2/day with the Daily×5 regimen.

Beyond 6 cycles, treatment should continue at the dose level reached as long as the subject continues to benefit based on investigator judgment and subject response and tolerability.

7.3.2 Guidelines for TC

For dose adjustment of TC therapies, refer to the latest locally-approved Prescribing Information for each therapy (USA examples: Cytarabine 2008, Dacogen 2010, Vidaza 2014) in the relevant region. Dose adjustments should be made according to institutional standards and relevant locally approved Prescribing Information.

7.4 Emergency Treatment for Subjects with Highly Proliferative Progressive AML

This study allows enrollment of subjects with proliferative AML (total WBC count ≥20,000). For those subjects, pretreatment with hydroxyurea or leukapheresis before randomization may be warranted to decrease total WBC count. However, hydroxyurea, leukapheresis, or other anti-leukemia therapy is not allowed after subjects are randomly assigned to study treatment. After the first cycle of study treatment, subjects who continue to have rapidly increasing total WBC counts with increasing PB blasts % are allowed to start the next study treatment cycle earlier than Day 29. Early administration of study treatment allows such subjects to remain on study and potentially benefit from treatment. Benefit may require multiple cycles given the lower intensity treatments in this study (as compared with intensive remission induction therapy).

Any deviation from the study schedule should be clearly explained and documented in the eCRF. After the proliferative phase subsides and the subject responds to treatment, the standard treatment cycle duration of 28 days should be resumed and maintained.

7.5 Concomitant Treatment

On the concomitant medication CRF/eCRF, document all medications a subject takes, starting from 14 days before randomization and ending 30 days after the last dose of study treatment. Include supportive or palliative treatment (see below), whether prescription or nonprescription, and medications taken for procedures (eg, biopsy). Include start and stop dates and indication.

7.5.1 Supportive, Prophylactic, or Other Treatments

The investigator is permitted to prescribe supportive treatment(s) at his or her discretion. Appropriate hydration and supportive care, including blood and platelet transfusions, may be administered according to study-center standards. Aggressive surveillance, prophylaxis, and/or treatment of bacterial, fungal, viral, and opportunistic infections are essential to prevent morbidity and mortality. Any supportive treatment or infusion should be documented in the provided CRFs/eCRFs.

7.5.1.1 Antibiotics or Anti-fungals

Antibiotics and/or anti-fungals may be used to manage febrile neutropenia based on institutional standard practice.

7.5.1.2 Hematopoietic Growth Factors

Use is permitted if deemed to be medically necessary by the treating physician and should be guided by accepted practice or institutional guidelines.

7.5.1.3 Hydroxyurea and/or Leukapheresis

Hydroxyurea and/or leukapheresis will be allowed for all subjects before randomization to reduce WBC counts in subjects with highly proliferative disease. Hydroxyurea and leukapheresis are prohibited after randomization. If, after initiation of study treatment, a subject's disease remains highly proliferative, where WBC counts and blast % are high and start to rise again before Day 28, the investigator may administer the subsequent treatment cycle earlier than Day 28 as described in Section 7.4. This should be documented in the eCRF.

7.5.2 Prohibited Concomitant Treatment

Other anticancer therapies, unless specified in the protocol, are not to be used. Cytotoxic chemotherapy and investigational treatments are prohibited for as long as subjects remain on study treatment.

Vaccination with live vaccines is prohibited while subjects remain on study treatment.

7.6 Overdose Instructions

Record the actual dose of study drug administered in the source document and on the Dosing CRF/eCRF. Record any adverse clinical signs and symptoms associated with a potential overdose on the AE CRF/eCRFs. Report signs and symptoms of a potential overdose that meet serious adverse event (SAE) criteria (defined in Section 10.1.2) to Astex on the SAE form within 24 hours (see Section 10.3). Treat any AE (including SAE) based on standard care for the specific signs and symptoms.

8.0 RISKS/PRECAUTIONS

Refer to the SGI-110 IB for the most current risks and precautions, as well as a complete list of AEs considered expected with SGI-110 therapy.

Common AEs observed in the AML/MDS population treated with SGI-110 include injection site AEs, febrile neutropenia, thrombocytopenia, anemia, diarrhea, fatigue, and nausea. The most common SAEs were febrile neutropenia and pneumonia. MDS and AML subjects commonly have severely compromised BM and blood counts. Severe or prolonged myelosuppression have been reported as related to SGI-110, particularly on high doses (ie, $\geq$125 mg/m^2). Two AML/MDS subjects (1 MDS and 1 AML of 357 subjects total) treated with SGI-110 had drug-related SAEs of sepsis with an outcome of death at doses of 125 mg/m^2/day for 5 days (MDS) and 18 mg/m^2/day for 5 days (AML).

Refer to Section 7.3 for guidelines to adjust study treatment dose.

Injection site reactions, such as pain, irritation, inflammation, erythema, and burning have been reported in the AML/MDS population and in subjects with solid tumors. Injection site reactions are related to SGI-110 SC administration. Care must be taken to avoid intradermal injection. Administer SGI-110 by slow SC injection. If injection site pain is reported upon injection, apply ice packs to the injection site both before and after injection. If injection site AEs are reported at subsequent injections despite slow injection and use of ice packs, pretreatment with topical or systemic analgesics can be considered.

Use of decitabine, the active metabolite of SGI-110, alters fertility and is mutagenic. Because of the possibility of infertility, men should seek advice on conservation of sperm, and women of child-bearing potential should seek consultation regarding oocyte cryopreservation before study treatment is started.

For risks and benefits of TC therapies, refer to the latest locally-approved Prescribing Information for each therapy (USA examples: Cytarabine 2008, Dacogen 2010, Vidaza 2014).

9.0 STUDY ASSESSMENTS AND PROCEDURES

9.1 Eligibility

Eligibility will be assessed by the investigator for the purpose of randomization and study entry; however, AML diagnosis will be confirmed by the central pathologist. Investigators are encouraged to request central pathologist confirmation of eligibility before randomization if they believe the AML diagnosis would be in doubt. Such confirmation will minimize the number of subjects the central pathologist may deem as having unconfirmed AML.

9.2 Efficacy

PB will be assessed at screening and on Day 1 of each cycle for response evaluation. BM aspirate or biopsy will be performed at screening then at the end of Cycles 2, 4, and 6 (Day 1 of Cycles 3, 5, and 7) unless PB shows persistence of leukemic blasts that excludes the possibility of a marrow response. After Cycle 6 BM assessment (Day 1 of Cycle 7), BM aspirate/biopsy will be repeated every 3 months for the first year on study and then every 6 months thereafter until PB or BM assessment shows disease progression or relapse.

CR will be assessed by modified IWG 2003 AML Response Criteria (see Section 11.6), based on blood sampling and BM aspirate/biopsy. Response assessment will be based on BM blinded review and the most concomitant PB counts. After blinded BM response is confirmed, assessment of normal count recovery will be done based initially on the most concomitant PB counts and in later cycles on PB counts from Day 1 of each cycle to avoid transient treatment-induced normal count suppression. The central pathologist who evaluates BM and PB counts for response assessment, as well as the central response reviewer, will be blinded to treatment assignment (Section 6.2).

9.3 Pharmacokinetics

PK parameters will be assessed using population PK analysis. At selected study centers, sparse PK samples will be collected within windows at the time points specified below (with time of sampling recorded).

For subjects who receive SGI-110, blood sample collection will be assigned to the following time points:

- Cycle 1, Day 1, at 1.5 hours (±30 minutes) and 3 hours (±1 hour) postdose.
  (1.5-hours sample is intended to be time-matched with the on-treatment ECG evaluation.)

AND

- Cycle 1, Day 5, at 1 hour (±30 minutes) and 5 hours (±2 hours) postdose.

For subjects in the TC group receiving decitabine IV, blood sample collection will be assigned to one of the following time points:

- Cycle 1, Day 1, at 30 minutes (±10 minutes) into the IV infusion, and then immediately before the end of infusion (at 1 hour).

OR

- Cycle 1, Day 5, immediately before the end of infusion (at 1 hour); and at 5 minutes (±2 minutes) and 3 hours (±1 hour) after the end of infusion.

9.4 Safety

Safety assessments will be based on AEs, concomitant medications, physical examination, vital signs, ECOG status, electrocardiogram (ECG) measurements, and clinical laboratory parameters (hematology and chemistry).

9.5 Study Procedures

9.5.1 Schedule of Events

Table 16 presents the complete schedule of events for the study, with details following in text. Additional information on the study procedures is provided in the study procedures manual.

Clinical and diagnostic laboratory evaluations are detailed before study entry, throughout the study, and at the follow-up evaluation. The purpose of obtaining these detailed measurements is to ensure adequate assessments of efficacy, safety, and tolerability. Repeat clinical evaluations and laboratory studies more frequently if clinically indicated.

Note any deviation from protocol procedures. Investigators are responsible for implementing appropriate measures to prevent the recurrence of violations and deviations and to report to their Institutional Review Board/Independent Ethics Committee (IRB/IEC) according to policy.

Table 16: Schedule of Events

Cycles (28 Days)		**1 and 2**												**≥3**													
Cycle Day		1	2	3	4	5	6	7	8[b] (±2)	9	10	15 (±3)	22 (±3)	1 (+7)	2	3	4	5	6	7	8[b]	9	10	15 (±3)	**Tx Dsc Safety FU[c]**	**Long Term Follow-Up[d]**
Study Treatment[b]																											
SGI-110 SC Days 1-5		X	X	X	X	X								X	X	X	X	X									
TC: Cytarabine SC BID Days 1-10		X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X				
TC: Decitabine IV Days 1-5		X	X	X	X	X								X	X	X	X	X									
TC: Azacitidine IV/SC Days 1-7		X	X	X	X	X	X	X						X	X	X	X	X	X	X							
Procedures	**Screening[a] (D -14 to -1)**																										
Informed consent	X																										
Medical history, including demographics	X																										
Eligibility assessments	X																										
Physical examination[e]	X	X[e]												X[e]											X		
Vital signs[f]	X	X	X	X	X	X	X[f]	X[f]	X[f]	X[f]	X[f]			X	X	X	X	X	X[f]	X[f]	X[f]	X[f]	X[f]		X		
ECOG performance status	X	X												X											X		
12-lead ECG (triplicate)[g]		X																							X		
Health-related QOL (EQ-5D-5L)[h]		X												X											X	X[d]	
Height	X																										
Weight and BSA calculation (use height from screening)[i]		X												X													
AEs/concomitant medications[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Randomization (before dosing)	X[a]																										

Table 16: Schedule of Events (Contd)

Cycles (28 Days)		1 and 2												≥3													
Cycle Day		1	2	3	4	5	6	7	8[b] (±2)	9	10	15 (±3)	22 (±3)	1 (+7)	2	3	4	5	6	7	8[b]	9	10	15 (±3)	Tx Dsc Safety FU[c]	Long Term Follow-Up[d]
Laboratory Assessments	**Screening[a] (D -14 to -1)**																									
Hematology[k]	X	X[k]							X			X	X	X[k]										X[k]	X	X[d]
Serum chemistry[l]	X	X[l]												X[l]											X	
Urinalysis	X																									
Serum or urine pregnancy test[m]	X	X												X											X	
Pharmacokinetics (PK)[n]		X				X																				
Molecular genetics and cytogenetics[o]	X																									
Disease Assessments																										
BM aspirate or biopsy[p]	X													X												X[d]
Hospitalizations/Transfusions[q]	X	X							X			X	X	X										X	X	X[d]
Subsequent anti-leukemia therapy																									X	X
Disease progression status[r]																									X	X[d]
Survival follow-up																										X

a. **Screening (and Randomization):** Screening must occur within 14 days of randomization, except that BM aspirate/biopsy and molecular genetics/cytogenetics will be collected within 28 days before Cycle 1 Day 1. Randomization should occur as close as possible to Cycle 1 Day 1 and may occur on Cycle 1 Day 1. A maximum of 1 week between randomization and treatment is allowed.

b. **Study Treatment**: Dosing days are consecutive according to approved prescribing information.

c. **Treatment discontinuation and safety follow-up (Tx Dsc Safety FU) visit:** Must occur 30 (+7) calendar days after the last dose of study treatment. If the subject cannot attend the clinic, the visit may be conducted by telephone to collect, at minimum, AE information.

d. **Long-term follow-up visits:** Start after treatment discontinuation. Monthly (±7 days) visits are required for subjects who discontinue study treatment before Cycle 6, until 6 months after the start of study treatment. After monthly visits for at least 6 months, long-term follow-up visits will be every 3 months (±2 weeks) until death. Health-related QOL, hospitalizations, and transfusions are done only at monthly visits. Hematology, BM aspirate or biopsy, and disease progression assessment are done only for subjects who have not progressed at treatment discontinuation. Visits may be conducted by telephone.

e. **Physical examination:** Complete physical examination includes weight and examination of body systems according to institutional standards. A complete physical examination is required. Day 1 physical examination does not need to be repeated if it was done within 4 days.

f. **Vital signs:** Assess before dosing on every dosing day in the clinic (ie, Days 6 and 7 only for TC therapies cytarabine and azacitidine, and Days 8-10 only for cytarabine), after subject has rested in the sitting position for at least 3 minutes. Vital signs include blood pressure (systolic/diastolic), respiration rate, heart rate, and body temperature. If dosing is done at home (according to local standards), vital sign assessment is not required.

g. **12-Lead ECG (triplicate):** ECGs in triplicate will be conducted predose and 1-2 hours postdose only on Day 1 of Cycle 1, and at study treatment discontinuation. Acquired and reviewed according to institutional procedure (rhythm, atrial rate, ventricular rate, PR interval, QRS duration, and QT/QTc, morphology and overall interpretation). The QT correction method should be the same for all ECGs for a given subject. Clinically significant abnormal ECG at study treatment discontinuation as compared to the predose ECG should be followed for recovery or stabilization.

h. **Health-related QOL**: Administer EQ-5D-5L (see Appendix 4) before treatment on Day 1 of each cycle. For subjects who discontinue treatment before Cycle 6, administer EQ-5D-5L at monthly visits until 6 months after the start of study treatment. Not required for visits every 3 months in long-term follow-up.

i. **Weight and BSA (body surface area) calculation:** Weigh subjects on Day 1 of each cycle. BSA recalculation is only required if weight changes ±10% or more from screening.

j. **Concomitant medications:** Document all concomitant medications within 14 days before randomization to 30 days after the last dose of study treatment.

k. **Hematology:** Include complete blood count with manual differential. Day 1 hematology for all cycles does not need to be repeated if done within 4 days of Day 1. For Cycles >6, hematology will be required only on Day 1. Additional hematology assessment may be done for safety or for subject management at the investigator's discretion. Collection, analysis, and reporting information are described in the Study Lab Manual.

l. **Serum chemistry:** Refer to Table 17. Day 1 chemistry for all cycles does not need to be repeated if done within 4 days of Day 1. Additional chemistry assessment may be done for safety or for subject management at the investigator's discretion. Collection, analysis, and reporting information are described in the Study Lab Manual.

m. **Pregnancy test:** Women of child-bearing potential only. The screening test must be done within 7 days of Cycle 1 Day 1 (ie, Day -7 to -1); test not required on Cycle 1 Day 1 if done at screening.

n. **PK:** At selected study centers: Subjects receiving SGI-110 and subjects in the TC group who receive decitabine IV in Cycle 1 only. Refer to Section 9.3 for details.

o. **Molecular genetics and cytogenetics:** BM and blood samples will be collected within 28 days before starting study treatment to evaluate cytogenetics (chromosome abnormalities) and gene mutations (such as FLT3-ITD, NPM1, CEBPA).

p. **BM aspirate or biopsy:** BM aspirate and/or biopsy differential count will be performed according to local standard practice. The screening aspirate must be collected within 28 days before starting study treatment. If BM aspirate/biopsy was completed before consent for this study, center must be able to obtain slides for central reader and samples for screening cytogenetic assessments. A biopsy should be done if no spicules are observed in the aspirate. Marrow aspirate or biopsy differential may include the following:

- Total cells counted
- Blasts
- Promyelocytes
- Myelocytes
- Metamyelocytes
- Segmented neutrophils
- Eosinophils
- Basophils
- Lymphocytes
- Plasma cells
- Monocytes
- Pronormoblasts
- Normoblasts
- M:E ratio
- Auer rods
- Megakaryocytes: increased, normal, decreased, absent
- Presence of dysplasia: dysE, dysG, dysM
- Cellularity: % cellularity: hypocellular, hypercellular, normocellular
- Other

Slides should be Wright Giemsa or May Grunwald Giemsa stained. Send 1 or 2 PB and BM slides for each subject at each time point. Detailed instructions on collection, labeling and shipping are described in the Study Lab Manual. A BM sample adequate for analysis must be obtained. Repeat the BM sample if not interpretable.

Response assessment is done on Day 1 of Cycles ≥2 based on BM aspirate/biopsy and the most concomitant PB. Assess PB at screening and on Day 1 of each cycle. Perform BM aspirate/biopsy at screening and then at the end of Cycles 2, 4, and 6 (ie, Day 1 of Cycles 3, 5, and 7 [±7-day window]) unless PB shows persistence of leukemic blasts that excludes the possibility of a marrow response. After blinded BM response is confirmed, assessment of normal count recovery is done based initially on the most concomitant PB counts and in later cycles on PB counts from Day 1 of each cycle to avoid transient treatment-induced normal count suppression. Subjects who discontinue treatment before Cycle 6 Day 1 before documented disease progression must undergo response assessment until disease progression or relapse is confirmed. After Cycle 6,

repeat BM aspirate/biopsy every 3 months for the first year on study and then every 6 months thereafter until PB or BM assessment shows disease progression or relapse. Refer to Section 9.2.

q. **Hospitalizations/Transfusions:** Document all blood and platelet transfusions (blood product transfused and units) within 28 days before starting study treatment. Document all hospital admission and discharge dates and main reason for hospitalization, as well as all blood and platelet transfusions (blood product transfused and units), from Cycle 1 Day 1 and then monthly to 6 months after the first dose or to the Tx Dsc Safety FU visit, whichever is later. Not required for visits every 3 months in long-term follow-up.

r. **Disease progression status:** For subjects who discontinue study treatment before disease progression is documented, PB and BM aspirate/biopsy assessments as described in footnote "p" should continue until disease progression or relapse is confirmed.

9.5.2 Screening and Baseline Procedures

After the investigator or sub-investigator confirms that a subject is eligible and willing to participate in the study, study center personnel will randomly assign the subject to study treatment according to the study procedures manual.

Within 14 days before randomization (unless otherwise specified), perform the following study procedures and tests:

- Written informed consent. The ICF must be signed and dated by the subjects before any study-specific samples are collected or study-specific procedures are initiated.
- Complete medical history, including demographics. Record disease history, including the date of initial diagnosis and list prior treatments and responses to these treatments. Document concurrent medical signs and symptoms to establish baseline conditions. Prior treatments for MDS or other hematologic disorder, CMML, and AML should be recorded.
- Investigator's confirmation of eligibility. Perform all necessary procedures and evaluations to document that the subject meets each eligibility criterion.
- Complete physical examination including weight and examination of body systems according to institutional standards.
- Vital signs include resting systolic/diastolic blood pressure, resting respiration rate, resting heart rate, and body temperature.
- ECOG performance status.
- Height measurement (for BSA calculation).
- All study-procedure-related AEs from the time of informed consent.
- Record concomitant medications within 14 days before randomization.
- Blood and urine sample collection for laboratory assessments. (See Table 17)
- Serum or urine pregnancy test: for women of child-bearing potential only, collected within 7 days before starting study treatment. Results must be negative for the subject to be eligible for enrollment into the study.
- Blood sample collection for cytogenetics and molecular genetics, collected within 28 days before starting study treatment.
- BM aspirate or biopsy for baseline disease assessment, cytogenetics, and molecular genetics, collected within 28 days before starting study treatment.
- All blood and platelet transfusions (blood product transfused and units) within 28 days before starting study treatment.
- Study treatment randomization, after eligibility is confirmed. Randomize as close as possible to the first dose of study treatment (on Cycle 1 Day 1), within a maximum of 1 week from Cycle 1 Day 1.

Table 17: Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Serology
• Complete blood count (CBC) - Hemoglobin - Hematocrit - RBC counts - WBC counts - Platelets • WBC differential - Blasts - Promyelocytes - Myelocytes - Metamyelocytes - Monoblasts - Promonocytes - Neutrophils - Band neutrophils - Segmented neutrophils - Eosinophils - Basophils - Lymphocytes - Monocytes	• Albumin • Alkaline phosphatase • Alanine transaminase • BUN • Calcium • Chloride • Creatinine • Glucose • Magnesium • Potassium • Sodium • Total bilirubin • Direct bilirubin (only if medically indicated) • Total protein	• Dipstick (analysis based on institutional standards) • Pregnancy test (if applicable)	• Pregnancy test (if applicable)

9.5.3 Treatment and Follow-up Procedures (Cycles 1 and 2)

The following text represents Cycles 1 and 2 assessments and procedures unless otherwise specified (PK and ECG assessments are done only in Cycle 1). Refer to Table 16.

9.5.3.1 Day 1 (Before Dosing)

- Complete physical examination (not required if done ≤4 days before Day 1).
- Vital signs.
- ECOG performance status.
- Triplicate 12-lead ECG (rhythm, atrial rate, ventricular rate, PR interval, QRS duration, and QT/QTc, morphology and overall interpretation).
- Health-related QOL by EQ-5D 5 level (EQ-5D-5L) (Appendix 4).
- Weight and BSA calculation (use height from screening; BSA recalculation if weight changes ±10% or more from screening).
- All study-procedure-related AEs and concomitant medications.
- Sample collection for laboratory assessments, including:
  - Hematology (see Table 17) (not required if done ≤4 days before Day 1).
  - Serum chemistry (see Table 17) (not required if done ≤4 days before Day 1).
  - Serum or urine pregnancy test (Cycle 2 only): for women of child-bearing potential only.

- Hospital admission and discharge dates (and the main reason for hospitalization), as well as all blood and platelet transfusions (blood product transfused and units), since the last visit.

9.5.3.2 Day 1 (During and After Dosing)

- 12-lead ECG (triplicate) in Cycle 1 only: at 1-2 hours postdose.
- At selected centers: sample collection for PK in Cycle 1 only: Refer to Section 9.3 for details about sampling.
  - For assigned subjects receiving SGI-110: postdose at 1.5 hours (±30 minutes) and 3 hours (±1 hour), with time of sampling recorded.
  - For assigned subjects receiving decitabine IV: at 30 minutes (±10 minutes) into the infusion, and then immediately before the end of infusion (at 1 hour)
- All treatment-emergent AEs and concomitant medications.

9.5.3.3 Dosing Days (Days 2-5, Days 2-7, or Days 2-10, Depending on Study Treatment)

- Vital signs (before dosing).
- All AEs and concomitant medications.
- Cycle 1 only: At selected centers: Day 5 sample collection for PK: Refer to Section 9.3 for details about sampling.
  - For assigned subjects receiving SGI-110: postdose at 1 hour (±30 minutes) and 5 hours (±2 hour), with time of sampling recorded.
  - For assigned subjects receiving decitabine IV: immediately before the end of infusion (at 1 hour); and at 5 minutes (±2 minutes) and 3 hours (±1 hour) after the end of infusion, with time of sampling recorded.

9.5.3.4 Days 8, 15, and 22

- All AEs and concomitant medications.
- Hematology (see Table 17).
- Hospital admission and discharge dates (and the main reason for hospitalization), as well as all blood and platelet transfusions (blood product transfused and units), since the last visit.

9.5.4 Treatment and Follow-up Procedures for Cycles ≥3

Table 16 shows assessments and procedures for Cycles ≥3.

9.5.4.1 Day 1 (Before Dosing), Cycles ≥3

Day 1 for Cycles ≥3 has a visit window of +7 days, unless otherwise specified below.

- Complete physical examination (not required if done ≤4 days before Day 1).
- Vital signs.
- ECOG performance status.
- Health-related QOL EQ-5D-5L (Appendix 4).
- Weight and BSA calculation (use height from screening; BSA recalculation if weight changes ±10% from screening).
- All AEs and concomitant medications.
- Sample collection for laboratory assessments, within 4 days of Day 1, including:
  - Hematology (see Table 17).
  - Serum chemistry (see Table 17).
  - Serum or urine pregnancy test: for women of child-bearing potential only.
- BM aspirate/biopsy required at the end of Cycles 2, 4, and 6 (Day 1 of Cycles 3, 5, and 7, ±7 days) unless PB shows persistence of leukemic blasts that excludes the possibility of a marrow response. After BM assessment at the end of Cycle 6 (Day 1 of Cycle 7), repeat BM aspirate/biopsy every 3 months for the first year on study and then every 6 months thereafter until PB or BM assessment shows disease progression or relapse. (See Section 9.2.)
- Hospital admission and discharge dates (and the main reason for hospitalization), as well as all blood and platelet transfusions (blood product transfused and units), since the last visit.

9.5.4.2 Dosing Days (Days 2-5, Days 2-7, or Days 2-10, Depending on Study Treatment), Cycles ≥3

- Vital signs (before dosing).
- All AEs and concomitant medications.

9.5.4.3 Day 15 (Cycles ≥3)

- All AEs and concomitant medications.
- Hematology (see Table 17).
- Hospital admission and discharge dates (and the main reason for hospitalization), as well as all blood and platelet transfusions (blood product transfused and units), since the last visit.

9.5.5 Treatment Discontinuation and Safety Follow-up Visit

Each subject should be followed up, to document the occurrence of any new AEs, for at least 30 (+7) days after his or her last dose of study treatment, or until any AE or SAE assessed as related to study treatment or procedures has resolved to a clinically acceptable or stable resolution (see Section 10.4). Subjects who withdraw consent should still be encouraged to complete this visit. The following evaluations are to be performed:

- Complete physical examination.
- Vital signs.
- ECOG performance status.
- 12-lead ECG (triplicate).
- Health-related QOL EQ-5D-5L (Appendix 4).
- All AEs and concomitant medications.
- Sample collection for clinical laboratory tests, including:
  - Hematology (see Table 17).
  - Serum chemistry (see Table 17).
- Serum or urine pregnancy test: for women of child-bearing potential only.
- Hospital admission and discharge dates (and the main reason for hospitalization), as well as all blood and platelet transfusions (blood product transfused and units), since the last visit.
- Subsequent anti-leukemia therapy (regimen and start date).
- Disease progression status (subjects who discontinue treatment before documented disease progression must undergo PB and BM aspirate/biopsy assessments until disease progression or relapse is confirmed).

The treatment discontinuation and safety follow-up visit may be conducted by telephone if needed to collect, at minimum, AE information.

9.5.6 Long-term Follow-Up

Long-term follow-up starts after subjects discontinue study treatment. Long-term follow-up visits will be either monthly or every 3 months, depending on when the subject discontinues study treatment:

- For subjects who discontinue treatment before Cycle 6, initial follow-up visits will be conducted monthly (±7 days) until 6 months after the start of study treatment, and then visits will be conducted every 3 months (±2 weeks), until death.
- For subjects who discontinue treatment after Cycle 6, long-term follow-up visits are required every 3 months (±2 weeks), until death.

Monthly long-term follow-up procedures (for subjects who discontinue treatment before Cycle 6):

- Health-related QOL EQ-5D-5L (Appendix 4).
- Hospital admission and discharge dates (and the main reason for hospitalization), as well as all blood and platelet transfusions (blood product transfused and units), since the last visit.
- Subsequent anti-leukemia therapy (regimen and start date).
- For subjects with no documented disease progression on treatment:
  - Hematology and/or BM aspirate/biopsy (≥1 year after the start of study treatment, BM aspirate/biopsy every 6 months) until disease progression or relapse is documented.
  - Disease progression status.
- Survival follow-up.

Long-term follow-up procedures for visits every 3 months (±2 weeks) (for subjects who discontinue treatment after Cycle 6 and for subjects have completed the monthly long-term follow-up visits described above):

- Subsequent anti-leukemia therapy (regimen and start date).
- For subjects with no documented disease progression:
  - Hematology and/or BM aspirate/biopsy (≥1 year after the start of study treatment, BM aspirate/biopsy every 6 months).
  - Disease progression status.
- Survival follow-up.

Long-term follow-up visits may be conducted by telephone if needed.

9.6 Unscheduled Visits

Additional visits (not specified in Table 16) may be conducted for PB assessment, BM aspirate/biopsy, chemistry assessment, or AE evaluation, at the investigator's discretion.

9.7 Missed Evaluations

Evaluations should occur within the visit window specified by the protocol. If an evaluation is missed, reschedule and perform it as close as possible to the original date. If rescheduling becomes, in the investigator's opinion, medically unnecessary because the evaluation would occur too close to the next scheduled evaluation, it may be omitted.

10.0 EVALUATION, RECORDING, AND REPORTING OF ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Event (AE)

Adverse Event (AE): Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal finding in laboratory tests or other diagnostic procedures), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug and from any route of administration, formulation, or dose, including an overdose.

Disease progression is not considered to be an AE or SAE. If there are specific AEs that are always part of disease progression, these do not need to be reported as AEs or SAEs. Pre-existing medical conditions (other than natural progression of the disease being studied) judged by the investigator or subject to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period will be reported as AEs or SAEs as appropriate.

An AE or SAE can also be a complication that occurs as a result of protocol mandated procedures (eg, invasive procedures such as biopsies).

10.1.2 Serious Adverse Events (SAEs)

An AE is considered serious, if in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death.
- A life-threatening AE.

  An AE is considered "life-threatening" if in the view of either the investigator, or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of an existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.

Important medical events that may not result in death, be life-threatening or require hospitalization may be considered serious when, based on the appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE. Examples of such medical events are intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or development of drug dependency or drug abuse. For clarification, Grade 3 or 4 cytopenias that are not associated with a life-threatening or otherwise medically

significant clinical AE as defined above, and do not result in hospitalization, are not considered SAEs.

10.2 Adverse Event Reporting and Descriptions

Record new AEs from the start of study treatment until 30 days after the last dose of study treatment (ie, discontinuation of treatment in the study) or until the subject starts new anti-leukemic treatment, including new investigational treatment. Also record screening procedure-related AEs that occur before the start of study treatment.

Record all treatment-emergent AEs (AEs occurring after the start of study treatment) either observed by the investigator or one of his or her medical collaborators, or reported by the subject spontaneously, or in response to the direct question below, in the AEs section of the subject's CRF/eCRF, in the source document, and if applicable, record on the SAE form. Whenever possible, the investigator should group signs and symptoms (including laboratory tests or other results of diagnostic procedures) into a single diagnosis under a single term. For example, cough, rhinitis, and sneezing might be reported as "upper respiratory infection" or a pulmonary infiltrate, positive sputum culture and fever might be reported as "pneumonia."

To optimize consistency of AE reporting across centers, ask the subject a standard, general, non-leading question to elicit any AEs (such as "Have you had any new symptoms, injuries, illnesses since your last visit?").

Death is an outcome of an SAE and usually not itself an SAE, unless it is death with no identifiable cause or event. In all other cases, record the cause of death as the SAE. Investigators will assess the status of previously reported, and occurrence of new, AEs and SAEs at all subject evaluation time points during the study.

10.2.1 Severity

Use the definitions found in the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 for grading the severity (intensity) of AEs (Appendix 3). The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE v4.03, use the following grading system to assess severity:

- Grade 1 – Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 – Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL), such as preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- Grade 3 – Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL, such as bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
- Grade 4 – Life-threatening consequences; urgent intervention indicated.
- Grade 5 – Death related to AE.

10.2.2 Relationship to Study Treatment (Suspected Adverse Reactions)

Assess all AEs/SAEs for relationship to study treatment or if applicable, to study procedure.

If an AE/SAE occurs before the first dose of study treatment, report it only if it is considered related to a study-specific procedure (eg, bleeding or local infection after skin punch biopsy). Those events will be recorded in the study database but will not be part of the treatment-emergent AE analysis.

To ensure consistency of AE and SAE causality assessments, investigators should apply the general guideline shown below. Multi-drug regimens should have a causality assessment of each component to aid in analysis.

Related (Suspected Adverse Reaction)	A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE such as a plausible temporal relationship between the onset of the AE and administration of the drug; and/or the AE follows a known pattern of response to the drug; and/or the AE abates or resolves upon discontinuation of the drug or dose reduction and, if applicable, reappears upon rechallenge. Further examples of type of evidence that would suggest a causal relationship between the drug and the AE: • A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome), • One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (eg, acute myocardial infarction in a young woman), • An aggregate analysis of specific events observed in a clinical study (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group that in a concurrent or historical control group.

Not Related (Not Suspected)	Adverse events that do not meet the definition above.

10.2.3 Pregnancy and Abortion

Report any pregnancy that occurs in a subject or male subject's female partner during the time between the first study-specific procedure and 60 days after the last dose of study treatment. Record any occurrence of pregnancy on the Pregnancy Report Form Part I and send to Astex Pharmaceuticals Drug Safety within 24 hours of learning of the event. After the birth of the baby, collect additional information on the baby until the baby is 1 year old by completing the Pregnancy Report Form Part II.

A subject must immediately inform the investigator if the subject or subject's partner becomes pregnant during the time between the first study-specific procedure and 60 days after the last dose of study treatment. Any female subjects receiving study treatment who become pregnant must immediately discontinue study treatment. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Report any abortion and the reason for it, whether therapeutic, elective, or spontaneous, to Astex Pharmaceuticals Drug Safety within 24 hours, through the SAE reporting process (Section 10.3).

10.3 Reporting and Evaluation of Serious Adverse Events

10.3.1 Reporting Requirements for Serious Adverse Events (SAEs)

All SAEs regardless of causality will be reported by the investigator to Astex Pharmaceuticals through the 30-day period after the last dose of study treatment. Deaths and SAEs occurring after the 30-day safety follow-up period AND considered related to study treatment or study procedures must also be reported.

Report all SAEs (initial and follow-up information) on an SAE form and send the form to Astex Pharmaceuticals Drug Safety, or designee, within 24 hours of the discovery of the event or information (see below). Astex Pharmaceuticals may request follow-up and other additional information from the investigator (eg, hospital admission or discharge notes, laboratory results).

Astex Pharmaceuticals Drug Safety Contact Information	
PRIMARY CONTACT: Email	[redacted]
Global Phone	[redacted]
North America Toll-Free Fax	[redacted]

Report all deaths with the primary cause of death as the SAE term, as death is the outcome of the event, not the event itself. If an autopsy was performed, report the primary cause of death on the autopsy report as the SAE term. Forward autopsy and postmortem reports to Astex Pharmaceuticals Drug Safety, or designee, as outlined above.

If study treatment is discontinued, temporarily suspended, or dose reduced because of an SAE, include this information in the SAE report.

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that qualify for mandatory expedited reporting to regulatory authorities where the SAE is suspected to be caused by the study treatment and is considered unexpected (ie, not defined as expected in the current IB, clinical study protocol, or approved labeling for marketed drugs). In this case, Astex Pharmaceuticals Drug Safety or designee will report to the relevant regulatory authorities and forward a formal notification describing the SUSAR to investigators, according to regulatory requirements. Each investigator must then notify his or her IRB/IEC of the SUSAR as required by local regulatory authorities and in accordance with IRB/IEC policy.

10.4 Follow-up for Adverse Events

Follow-up all AEs and SAEs assessed as related to study treatment or study procedures that are encountered during the protocol-specified AE reporting period (1) to resolution, (2) until the investigator assesses the subject as stable and the event is following a clinically expected outcome, or (3) until the subject is lost to follow-up or withdraws consent.

11.0 STATISTICS

Statistical analyses will be performed by Astex Pharmaceuticals or its designee.

Data summaries and listings will be generated using SAS version 9.3 or a more recent version (SAS Institute Inc., Cary, NC, USA).

The statistical analysis plan and/or the clinical study report will provide additional details of the analysis, which may include details of missing and, if applicable, unused data, as well as additional sensitivity analyses of the primary and secondary variables. The clinical study report will describe deviations from the statistical analysis plan, if any.

11.1 Sample Size

By trial design, the overall (2-sided) alpha level of 0.05 is split between the co-primary endpoints of CR (0.04) and OS (0.01). A formal interim analysis will be performed only for OS using a group sequential boundary preserving an overall (2-sided) 0.01 alpha level. The sample size calculation for the primary analysis of CR is based on testing at the 0.04 nominal alpha level. If statistical significance is achieved for CR, hierarchically, the final analysis of OS will be conducted to preserve an overall 2-sided 0.05 alpha level, accounting for alpha spent at the interim analysis of OS, as described in Section 11.6.7 and Section 11.9. The sample size calculation for OS will be shown for the setting of a 2-sided 0.05 alpha level.

Assuming a CR rate of approximately 0.20 (Kantarjian, Thomas et al 2012; Fenaux et al 2010; Burnett et al 2007) for subjects treated in the TC group (all TC therapies combined) and assuming an increase in CR rate to 0.30 or higher can be achieved by treating subjects with

SGI-110, 800 subjects (400 per treatment group) will provide approximately 89% power to detect the overall difference of 0.10 when using a 2-sided Cochran Mantel-Haenszel test having 2-sided alpha level of 0.04. For the purpose of this sample size calculation, the constant CR rates of 0.20 and 0.30 for the TC and SGI-110 groups, respectively, are assumed for each stratum.

For survival, an analysis at 670 death events will provide 90% power to detect a hazard ratio of approximately 0.78 (a difference in median survival of 7 months in the TC group versus 9 months in the SGI-110 group), when using a 2-sided stratified log-rank test at an 0.05 alpha level. Accrual is expected to be uniform over a 21 month enrollment period, with an additional follow-up of 12 months. Hence, the assessment of survival needs approximately the same sample size of 800 subjects. Primary response and survival analyses will be performed after 670 death events have occurred. For the purpose of this sample size calculation, a constant hazard ratio of approximately 0.78 was assumed for all strata defined by the stratification factors.

11.2 Data Sets to be Analyzed

11.2.1 Efficacy

Efficacy analyses will be based on intent-to-treat (ITT) principle. The efficacy data set will include data from all subjects randomly assigned to study treatment. All data will be included and no subjects excluded because of protocol violations. For the analysis of efficacy data, subjects will be included in the treatment group according to their randomly assigned treatment. A secondary efficacy dataset will be analyzed for the co-primary endpoints of CR and OS based on treatment actually received.

For NDAOH, transfusions, and health-related QOL by EQ-5D-5L datasets, the primary analysis will include only the data collected during the first 6 months of the study because, during this study period, subjects are assessed whether or not they are still on study treatment. Secondary analysis datasets may also be analyzed (eg, over the period of study treatment).

11.2.2 Safety

The safety data set will include data from all subjects randomly assigned to study treatment who receive any amount of study treatment or any component of a multi-dose study treatment regimen. All data will be included and no subjects excluded because of protocol violations.

For safety data analysis, subjects will be included in the treatment group according to the treatment they actually receive.

11.2.3 Pharmacokinetics

The PK data set will include all available plasma concentrations and PK parameters for SGI-110 and decitabine from subjects at selected centers who have received SGI-110 or decitabine IV and for whom PK samples were collected and successfully analyzed. PK data will be analyzed using the PK data set.

11.2.4 Pharmacodynamics Analyses

Pharmacodynamics analyses are not applicable to this study.

11.3 Schedule of Analyses

Data listings and summary tables will be reviewed by the DMC approximately every 6 months to ensure the safety of study subjects and to enhance the quality of trial conduct (refer to Section 4.4). An interim analysis of OS will also be conducted by the DMC when approximately half of the required death events have occurred. All available study data will be analyzed after 670 death events have occurred to achieve a mature analysis of OS.

11.4 Disposition

The number and percentage (n, %) of subjects enrolled, treated, lost to follow-up, and withdrawn (with reason) will be summarized. Sample size for efficacy and safety analysis data sets will be clearly identified for each treatment group. All screened subjects will be included in the disposition analysis.

11.5 Analysis of Demographic and Baseline Data

Subject demographic and baseline characteristics will be summarized by mean, standard deviation, median, minimum, and maximum for continuous variables; and by counts and percentages for categorical variables. The Efficacy and Safety datasets will be used for the summaries. The summaries will be done for each treatment group and both treatment groups combined.

11.6 Efficacy Analyses

Efficacy analyses will be based on the Efficacy dataset. Unless otherwise specified, this section describes the analyses conducted at the primary analysis time point when 670 death events have occurred, assuming that the study continued after the planned interim analysis. The alpha levels referenced in this section are nominal alpha levels for judging statistical significance, taking into consideration the planned interim analysis and the hierarchical testing order of the (final) primary analysis. The overall experimental alpha error is controlled at the 2-sided 0.05 level.

The co-primary efficacy endpoints are

- CR rate by modified IWG 2003 AML Response Criteria (Cheson et al 2003) as described in Section 11.6.1. Assessments will be blinded as described in Section 11.6.1.
- OS, defined as the number of days from randomization to death.

If either of the co-primary efficacy endpoints reaches statistical significance in favor of SGI-110 at either the interim analysis (OS only) or final analysis (CR and OS), then the study will be considered positive in efficacy.

Secondary efficacy endpoints are the following and will be defined in more detail in the statistical analysis plan:

- CRc (CR+CRi+CRp) rate.
- NDAOH.
- PFS, defined as the number of days from randomization to disease progression or death, whichever occurs first.
- Number of RBC or platelet transfusions (units) over the duration of the study treatment.
- Health-related QOL by EQ-5D-5L (consisting of the EQ-5D-5L descriptive system and the EQ Visual Analogue Scale [EQ VAS]).
- Duration of CR, defined as the time from first CR to time of relapse.

11.6.1 Criteria for Response Assessment

Modified IWG 2003 Response Criteria (Table 18) will be used by an independent blinded reader to identify AML subjects with CR, CRp, CRi, or partial response. BM biopsy/aspirate and corresponding concomitant PB counts will be assessed by a blinded central pathologist, and all assessments of response will be reviewed and confirmed by an independent blinded central reviewer (either the same person who assessed pathology or a different blinded independent reviewer).

Table 18: Modified 2003 IWG AML Response Criteria

Response[a]	Peripheral Blood (PB)	Bone Marrow (BM)
CR	ANC ≥1000/μL, Platelets ≥100,000/μL, independence from RBC and platelet transfusions over the past week, no leukemic blasts[b]	<5% leukemic blasts
CRp	ANC ≥1000/μL, Platelets <100,000/μL, independence from RBC transfusions over the past week, no leukemic blasts[b]	<5% leukemic blasts
CRi	ANC <1000/μL, no leukemic blasts[b]	<5% leukemic blasts
Partial response	ANC ≥1000/μL, Platelets ≥100,000/μL, no leukemic blasts[b]	Decrease of ≥50% in leukemic blasts to level of 5% to 25%

[a] Responses are based on both PB and BM conditions.
[b] For the purpose of response assessment and according to published IWG criteria, blasts may be seen in PB as rare PB blasts may be identified during regeneration, but the subject is in CR if BM blasts are <5% with no Auer rods (Cheson et al 2003).
ANC=absolute neutrophil count; CR=complete response; CRp=complete response with incomplete platelet recovery; CRi=CR with incomplete blood count recovery.
Source: Cheson et al 2003

Subjects with these different response categories, as well as nonresponders and nonevaluable subjects described below, will be listed and summarized. In particular, best response will be used when a subject experienced different response levels at different visits. Response rate will be calculated for best response categories described below to assess overall efficacy observed.

- CR, CRp, CRi, partial response.
- Composite CR (CRc=CR+CRp+CRi).

Subjects who did not have a post-treatment efficacy assessment (ie, no BM or PB assessment) will be classified as nonevaluable for response presentations. These subjects will be included in the denominator of the ITT analysis for calculation of different response rates. Subjects who cannot be classified into a response category (CR, CRp, CRi, partial response) or the nonevaluable category will be classified as nonresponders.

11.6.2 Complete Response (CR)

The primary endpoint of CR rate will be calculated as the number of subjects with a best response of CR divided by the total number of subjects included in the efficacy analysis. The CR rate will be compared between the 2 treatment groups using a Cochran Mantel-Haenszel test at an alpha level of 0.04 stratified by age (<75 or ≥75 years), ECOG performance status (0-1 or 2-3), study center region (North America, Europe, ROW), and secondary AML (secondary to MDS or other antecedent hematologic disorder) or poor-risk cytogenetics (either, neither). A 2-sided *p* value of ≤0.04 will be judged as statistically significant. In addition, the Mantel-Haenszel weighted difference in CR rate between the 2 treatment groups and its 2-sided 96% CI will be provided.

11.6.3 Overall Survival (OS)

OS is defined as the number of days from the day the subject was randomly assigned to study treatment to the date of death (regardless of cause). Survival time will be censored on the last date the subject is known alive or lost to follow-up before reaching the event of death. As a separate sensitivity analysis, survival time will also be censored on the date the subject receives other anti-leukemia therapy such as chemotherapy or HCT.

OS will be estimated by a stratified Kaplan-Meier method and compared between the 2 treatment groups using a stratified log-rank test. If the CR rate analysis is significant, OS will be tested at an alpha level of 0.05; without a significant CR rate test result, OS will be tested at an alpha level of 0.01, as described in Section 11.6.7. The stratification variables will include age (<75 or ≥75 years), ECOG performance status (0-1 or 2-3), study center region (North America, Europe, ROW), and secondary AML or poor-risk cytogenetics (either, neither). The medians and quartiles of OS will be summarized.

In addition, the hazard ratio (HR) and the 95% (or 99%, as appropriate) CI will be estimated using a Cox proportional-hazard model with treatment group as the independent variable and stratified by the same randomization stratification factors as used for the log-rank test.

For the planned interim analysis, OS will be compared between the 2 treatment groups using a stratified log-rank test at an alpha level provided by the Lan-DeMets implementation of the O'Brien-Fleming monitoring guideline, as described in Section 11.9.

11.6.4 Composite CR (CRc)

The CRc rate is calculated as the number of subjects with a best response of CR, CRp, or CRi divided by the total number of subjects included in the efficacy analysis. The CRc rate will be compared between the 2 treatment groups using a Cochran Mantel-Haenszel test with the stratification variables the same as for CR and OS. If CR rate analysis and OS analysis are both significant, the CRc rate will be tested at an alpha level of 0.05; with a nonsignificant CR rate result (p>0.04) and a significant OS result at the 0.01 level, the CRc rate will be tested at an alpha level of 0.01. In addition, the 2-sided 95% (or 99%, as appropriate) CI for the Mantel-Haenszel weighted difference in CRc rate between the 2 treatment groups will be provided.

11.6.5 Number of Days Alive and Out of the Hospital (NDAOH)

The date of each hospital admission and discharge will be collected for each subject. The average NDAOH will be summarized by treatment group and compared between the 2 treatment groups using a 2-sample t-test at an alpha level of 0.05 or 0.01 as appropriate, if the CRc test result is significant at that required level.

11.6.6 Progression-free Survival (PFS)

Progression is defined as the earliest occurrence of one of the following:

- For subjects with CR, CRi, or CRp, the confirmed (at least 2 PB samples at least 1 week apart) appearance of leukemic blasts in PB by investigator or central assessment, OR ≥5% leukemic blasts in the BM by blinded central pathologist assessment.
- For all other subjects, when PB or BM shows evidence of continued increase in blasts % that necessitates alternative therapy.
- Death.

PFS is defined as the number of days from randomization to the earliest date of investigator's assessment of disease progression or relapse by PB assessment or blinded BM assessment, whichever occurs first, or death (regardless of cause). PFS time will be censored on the last date the subject is known to be alive without a relapse/disease progression. Subjects receiving other anti-leukemia therapy before occurrence of a relapse/ disease progression will also be censored at the date of the start of other anti-leukemia therapy.

PFS will be compared between the 2 treatment groups using a stratified log-rank test at an alpha level of 0.05, or 0.01, as appropriate, if CRc and NDAOH test results are significant at that required level. The medians and quartiles of PFS will be summarized.

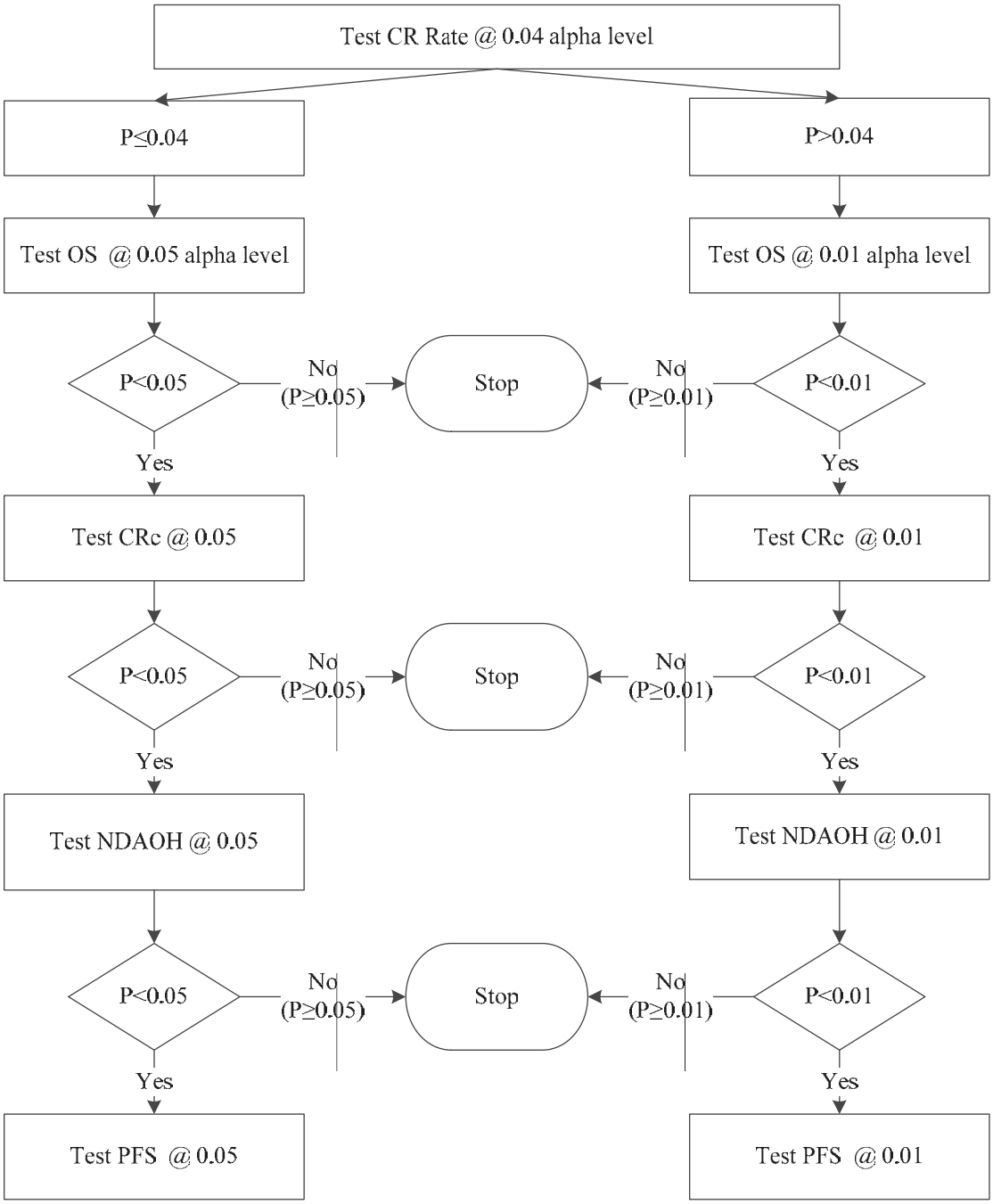
11.6.7 Test Sequence and Procedures of Statistical Tests for Efficacy Endpoints

To control the alpha errors associated with testing the multiple endpoints of CR rate, OS, CRc rate, NDAOH, and PFS, the following test sequence and procedures will be followed, assuming that the study continues after the planned interim analysis.

The primary efficacy variable CR rate will be tested first in the sequence at an alpha level of 0.04. If this test is positive (ie, $p \leq 0.04$), then analysis will proceed to the test for the co-primary efficacy variable of OS at the 0.05 alpha level. A positive CR analysis ($p \leq 0.04$) serves as a gatekeeper (Westfall and Krishen 2001) for proceeding to the analysis of OS at the 0.05 level. If the test for CR is not significant at the 0.04 level, the co-primary efficacy variable of OS will be tested at an alpha level of 0.01.

If the test for OS is positive at the 0.05 level, analysis will proceed to the test for the secondary efficacy variables of CRc rate, NDAOH, and PFS (in that order) at an alpha value of 0.05. For testing the secondary efficacy variables, CRc rate will be tested first. If the test for CRc rate is positive, then analysis will proceed to the test for NDAOH at the 0.05 alpha level; if the test for NDAOH is positive, then analysis will proceed to the test for PFS at a 0.05 alpha level. Similar to the primary endpoint analyses, a positive (ie, $p<0.05$) test result of a secondary endpoint tested earlier in the sequence serves as a gatekeeper for proceeding to the subsequent secondary analyses. If the test for CR is not significant at the 0.04 level, but the test for OS is significant at the 0.01 level, the secondary efficacy variables of CRc, NDAOH, and PFS will be tested hierarchically at an alpha level of 0.01. The hierarchical test order and alpha value to be used for each test at the primary analysis time point are further described in Figure 4.

Figure 4: The Hierarchical Test Order and Related Alpha Values



The overall alpha error rate is controlled at the 0.05 level by following the above testing sequence and procedures.

Other secondary efficacy endpoints (number of transfusions, health-related QOL, and duration of CR) will be used as supportive evidence of the beneficial treatment effect. The 95% CIs for these endpoints, if applicable, will be constructed.

11.6.8 Number of Red Blood Cell (RBC) or Platelet Transfusions

One transfusion is defined as 1 unit of RBC or 1 unit of platelets. Dates and the number of RBC or platelet transfusions will be collected for each subject. The average number of RBC or separately platelet transfusions per month will be summarized by treatment group. In addition, the number of RBC or platelet transfusions will also be summarized as a per-patient-year rate for each treatment group. The RR of these 2 per-patient-year rates (SGI-110 versus TC) and the associated 95% CI will be provided.

11.6.9 EQ-5D-5L

The calculation for EQ-5D-5L (EQ-5D-5L descriptive system and EQ VAS; Appendix 4) scores (health profile, self-rated health status, and index value) will be performed according to EuroQol group (http://www.euroqol.org/about-eq-5d.html; 2009). Change from baseline in EQ-5D-5L scores will be summarized by visit. A repeated measures analysis of variance model will be used to compare the groups for change from baseline in EQ-5D-5L scores.

11.6.10 Duration of CR

Duration of CR (in number of days) will be calculated from the first time a CR is observed to time of relapse (defined as the earliest time point whereby BM assessment or PB assessment [see Section 11.6.6] indicate relapse/disease progression due to reappearance of leukemic blasts in PB or ≥5% leukemic blasts in BM). The duration of CR will be censored at the last available time point at which a relapse/disease progression was not observed. Duration of CR will be estimated using the Kaplan-Meier method for subjects who achieved a CR during the study. To take the proportion of responders into consideration when analyzing duration of CR, a separate analysis including all subjects will be conducted with a 0-day event duration assigned to subjects who did not achieve a CR, with the 2 groups compared using a log-rank test.

11.6.11 Subgroup Analyses

Subgroup analyses will be performed to explore the influence of baseline variables, and the individual TC therapy administered, on the efficacy outcome of CR rate and OS, and to evaluate the treatment effect at different levels of each baseline variable. The analyses described in previous sections for these 2 outcome variables will be repeated for each level of the baseline variables and each TC therapy listed below:

- Age (<75, ≥75).
- AML category (primary, secondary).
- Baseline cytogenetic risk (poor-risk, others).
- Baseline ECOG PS (0-1 and 2-3).
- Baseline BM blasts (≤30%, >30%).
- Baseline total WBC counts (<20,000/μL, ≥20,000/μL).

- Study center region (North America, Europe, Asia-Pacific, Other).
- Race (White, Black, Asian, Other).
- Presence of baseline genetic abnormalities such as FLT3-ITD, NPM1, CEBPA (for each gene: yes, no).
- Individual TC (cytarabine, decitabine, azacitidine) compared with SGI-110 treatment.
- Additional subgroups may also be further described in the Statistical Analysis Plan.

11.7 Safety Analyses

Safety will be assessed by subject-reported and investigator-observed AEs and 30- and 60-day all-cause mortality, along with physical examination, clinical laboratory tests (hematology, chemistries), and ECGs. Safety variables will be tabulated and presented for all subjects who receive any amount of study treatment (SGI-110 or TC). Exposure to study treatment, reasons for discontinuation, deaths and causes of deaths will be tabulated. Treatment-emergent AEs (TEAEs) are defined as events that first occurred or worsened after the first dose of study drug given on Cycle 1 Day 1. TEAEs will be mapped to the appropriate System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs will be graded using CTCAE version 4.03.

Summaries will be provided for all AEs, AEs considered related to study treatment, SAEs, and related SAEs as follows:

- By maximum severity.
- Incidence by SOC (by severity grade and overall).
- Incidence by PT (by severity grade and overall) within each SOC.

The percentage of 30- and 60-day all-cause mortality will be calculated based on each subject's date of death relative to Course 1 Day 1 (C1D1; ie, date of death minus date of C1D1) and compared between the 2 treatment groups using a Chi-square test.

Laboratory values reported by different local labs will be listed. Laboratory values will also be graded, if possible, by CTCAE in conjunction with the Harrison (18^{th} edition) lab book normals (Longo 2011). Shift tables will display (1) shift from baseline grade to the worst grade, and (2) shift from baseline grade to the last grade.

Concomitant medication will be coded by the WHO Drug Dictionary and summarized by Therapeutic subgroup (ATC level 2) and PT, sorted alphabetically, using counts and percentages. Concomitant medications are the medications taken with a start date on or after the start of the administration of study treatment (C1D1), or those with a start date before the start of the administration of study treatment (C1D1) and a stop date on or after the start of the administration of study treatment (C1D1).

Vital signs will be summarized by visit using proportion of subjects with each vital sign being too high or too low according to conventionally accepted vital sign normal ranges. ECG data will be listed.

11.8 Pharmacokinetic Analyses

PK parameters will be derived using noncompartmental analyses for each subject for whom sparse PK samples were collected and successfully analyzed. Descriptive statistics will include mean, standard deviation, minimum, median, and maximum for SGI-110 and decitabine PK parameters.

The relationship between [redacted] will be assessed based on the PK data and efficacy/safety data collected in this study. The methods will include a population PK modeling approach using the sparse data collected. The details of population PK modeling and full results of the [redacted] analyses will be reported in a separate document, and the summary of key findings will be included in the clinical study report.

11.9 Interim Analysis

One formal interim analysis of OS is planned. This interim analysis will be conducted by the independent DMC after approximately half (ie, approximately 335) of the required death events have occurred. The nominal alpha value for the interim and final OS analyses is based on Lan-DeMets implementation of the O'Brien-Fleming boundary (Lan and DeMets 1983; O'Brien and Fleming 1979). With one interim analysis at 50% information time point plus one final analysis, the 2-sided alpha-boundaries are 0.00014 and 0.00995, respectively. If the trial continues after the interim analysis, and if the primary analysis of CR rate is significant at the 0.04 level, the alpha level for the primary analysis of OS will be 0.04+0.00995=0.04995≈0.05. If the trial continues after the interim analysis, and if the primary analysis of CR rate is not significant at the 0.04 level, the alpha value for the primary analysis of OS will be 0.00995≈0.01. The overall alpha error is controlled at the 0.05 level.

Refer to Section 11.3 for further details on the schedule of analyses.

11.10 Procedures for Handling Missing, Unused, and Spurious Data

No missing data imputations are planned for the study, except as specified. Subjects lost to follow-up will be included in statistical analyses to the point of their last evaluation.

12.0 STUDY DURATION

The expected study duration is approximately 36 months, including 21 months for completing enrollment and approximately 12-15 months follow-up before final analyses. The study is expected to start in Q1 2015 and end in Q1 2018.

13.0 STUDY COMPLIANCE AND ETHICAL CONSIDERATIONS

13.1 Compliance Statement

The study will be conducted in accordance with the ICH GCP guidelines; US Title 21 CFR Parts 11, 50, 54, 56, and 312; the EU Clinical Trials Directive and its successor; principles enunciated in the Declaration of Helsinki; and all human clinical research regulations in countries where the study is conducted.

13.2 Informed Consent

The ICFs used for the study must comply with the Declaration of Helsinki, federal regulations US 21 CFR Part 50, and ICH GCP guidelines and any other local regulations. The investigator, or a person delegated by the investigator, must explain the medical aspects of the study, including the nature of the study and the treatment, orally and in writing, in such a manner that the subject is aware of potential benefits and risks. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Subjects, or a legal guardian if the subject is unable to, must give informed consent in writing.

The informed consent process must be conducted, documented in the source document (including the date), and the form must be signed, before the subject undergoes any study-specific procedures.

13.3 Institutional Review Board or Independent Ethics Committee (IRB/IEC)

The investigator must submit the protocol, protocol amendments, and the ICF for the proposed study, along with any other documents required by the center's IRB/IEC to the center's duly constituted IRB/IEC for review and approval. The investigator must also ensure that the IRB/IEC reviews the progress of the study on a regular basis and, if necessary, renews its approval of the study on an annual basis. A copy of each IRB/IEC approval letter must be forwarded to the sponsor before the study is implemented. Documentation of subsequent reviews of the study must also be forwarded to the sponsor.

14.0 ADMINISTRATIVE PROCEDURES

14.1 Sponsor Responsibilities

Astex Pharmaceuticals reserves the right to terminate the study and remove all study materials from a study center at any time. Astex Pharmaceuticals and the investigators will assure that adequate consideration is given to the protection of the subjects' interests. Specific circumstances that may precipitate such termination are:

- Request by Health Authority to terminate the study.
- Unsatisfactory subject enrollment with regard to quality or quantity.

- Significant or numerous deviations from study protocol requirements, such as failures to perform required evaluations on subjects; maintain adequate study records; or inaccurate, incomplete, or late data recording on a recurrent basis.
- The incidence or severity of AEs in this or other studies indicating a potential health hazard caused by the study treatment.

14.1.1 Study Supplies

Refer to the SGI-110 -04 Study Procedures Manual for sponsor-provided supplies for this study.

14.1.2 Investigator Training

All study centers will have a center-specific study initiation meeting to ensure the center staff understand the protocol, study requirements, and data capture processes. This training will take place before the first subject is enrolled. Each study center will be provided with information regarding GCP and regulations specific to the conduct of clinical studies. Each center is responsible for ensuring that new team members are adequately trained and the training is documented.

14.1.3 Ongoing Communication of Safety Information during the Study

The sponsor will provide the investigator with documentation of SAEs, from this study and other studies, that are related to Astex IMP and unexpected (see Section 10.3.1), as appropriate. The investigator must forward this documentation to the IRB/IEC, as described in Section 10.3.1.

The sponsor will also notify the investigator about any other significant safety findings that could alter the safety profile of the IMP from what is described in the protocol and significantly affect the safety of subjects, affect the conduct of the study, or alter the IRB/IEC's opinion about continuation of the study. This does not include safety issues that could be mitigated by simple changes in the protocol decided by the DMC (Section 4.4) such as limiting some of the eligibility criteria or reducing the IMP dose or dosing schedule.

14.1.4 Study Monitoring

Representatives of Astex Pharmaceuticals will monitor the study. Routine monitoring visits will be conducted to:

- Assure compliance with the study protocol and appropriate regulations.
- Verify that (1) the informed consent process was conducted before initiation of any study-specific procedures (ie, performed solely for the purpose of determining eligibility for the study) and before provision of study treatment, and (2) this process is adequately documented.
- Verify that the protocol, protocol amendments, and safety information are submitted to the IRB/IECs and approved by the IRB/IECs in a timely manner.

- Review the CRF/eCRFs and source documents to ensure that reported study data are accurate, complete, and verifiable from source documents.
- Verify that study treatments are stored properly and under the proper conditions, that they are in sufficient supply, and that receipt, use, and return of SGI-110 at the study centers are controlled and documented adequately.
- Verify that the investigator and study center personnel remain adequately qualified throughout the study.
- Verify that the research facilities, including laboratories and equipment, are maintained adequately to safely and properly conduct the study.

14.1.5 Study Auditing and Inspecting

The sponsor may audit the study conduct, compliance with the protocol and accuracy of the data in one or more centers.

The investigator(s)/institution(s) will permit study-related monitoring, audits, and inspections by the sponsor, IRB/IEC, government regulatory bodies and Astex Pharmaceuticals Quality Assurance personnel or its designees by providing direct access to source data/documents after appropriate notification from sponsor.

14.2 Investigator Responsibilities

14.2.1 Subject Screening Log

The investigator must keep a record that lists all subjects who signed an informed consent and the reason for non-inclusion if they were not ultimately randomized or treated.

14.2.2 Study Treatment Accountability

An initial supply of SGI-110 will be shipped to each study center's pharmacy when all the initiation documents, including IRB/IEC approvals, IRB/IEC approved ICF, and business agreements, have been received and reviewed by Astex Pharmaceuticals and upon activation of the study center by Astex Pharmaceuticals.

Keep study treatment in a locked, limited-access room. The study treatment must not be used outside the context of the protocol. Under no circumstances should the investigator or other study center personnel supply study treatment to other investigators, subjects, or clinics or allow supplies to be used other than as directed by this protocol without prior authorization from Astex Pharmaceuticals.

The monitor will regularly review and verify all study treatment supplies and associated documentation.

Maintain an accurate accounting of the study treatments. These records must show dates, lot numbers, quantities received, dispensed, and returned and must be available for monitoring by the sponsor. The investigator will ensure that any used and unused study treatment and other study material is destroyed or returned to the sponsor on completion of the study. If the study treatment is destroyed at the study center, there should be documentation of destruction at the study center. The sponsor and/or their representatives will verify final drug accountability. Study treatment accountability records must be maintained and readily available for inspection by representatives of Astex Pharmaceuticals and are open to inspections by regulatory authorities at any time.

14.2.3 Reporting and Recording of Study Data

Data will be captured and compiled using procedures developed by the sponsor or their representatives. Clearly record all requested study data on the CRF/eCRF and other study forms as required. Whenever possible, record the reason for missing data in the source document. Only individuals who are identified on the study personnel responsibility/signature log may enter or correct data in the CRF/eCRF. Incomplete or inconsistent data on the CRF/eCRFs will result in data queries that require resolution by the investigator or designee.

The investigator must assure subject anonymity and protection of identities from unauthorized parties. On CRF/eCRFs or other documents or subject records provided to Astex Pharmaceuticals, identify subjects by code (subject number, initials, date of birth) and not by names. The principal investigator should maintain documents not for submission to Astex Pharmaceuticals (eg, subjects' signed informed consent) in strict confidence.

14.2.4 Source Documentation

The investigator must maintain adequate and accurate source documents upon which CRF/eCRFs for each subject are based. They are to be separate and distinct from CRF/eCRFs, except for cases in which the sponsor has predetermined that direct data entry into specified pages of the subject's CRF/eCRF is appropriate. These records should include detailed notes on:

- The oral and written communication with the subject regarding the study treatment (including the risks and benefits of the study). Record the date of informed consent in the source documentation.
- The subject's medical history before participation in the study.
- The subject's basic identifying information, such as demographics, that links the subject's source documents with the CRF/eCRFs.
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject.
- The subject's exposure to study treatment.
- All AEs.

- The subject's exposure to any concomitant therapy (including start and stop dates, route of administration, and dosage).
- All relevant observations and data on the condition of the subject throughout the study.

14.2.5 Tissue and Blood Sample Collection/Storage

Tissue and blood components samples which are collected as part of routine medical care or as part of protocol procedures may be stored and analyzed for PK or pharmacodynamic analyses.

After the study, samples may be used for additional investigation to help identify factors that may influence response to therapy. Such samples will be used in compliance with guidelines defined by FDA Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable (issued 25 April 2006) and European Agency for the Evaluation of Medicinal Products (EMEA)'s Reflection Paper on Pharmacogenomic Samples, Testing and Data Handling (EMEA 2007).

14.2.6 Records Retention

The investigator must ensure that clinical study records are retained according to national regulations, as documented in the clinical trial agreement entered into with the sponsor in connection with this study. The investigator will maintain all records and documents pertaining to the study including, but not limited to, those outlined above (see Section 14.2.4) for a period of: at least 2 years after FDA approval of the drug or at least 2 years after withdrawal of the IND under which this study was conducted, whichever is longer. In countries outside the US, records must be kept for the period of time required by the US FDA as a minimum, and record retention should also comply with the local country regulatory requirements, if longer retention times are required than in the US. Mandatory documentation includes copies of study protocols and amendments, financial disclosures, each FDA Form 1572, IRB/IEC approval letters, signed ICFs, drug accountability records, SAE forms transmitted to Astex Pharmaceuticals, subject files (source documentation) that substantiate entries in CRF/eCRFs, all relevant correspondence, and other documents pertaining to the conduct of the study. These records must remain in each subject's study file and be available for verification by study monitors at any time.

The investigator must inform the sponsor immediately if any documents are to be destroyed, transferred to a different facility, or transferred to a different owner. The sponsor should be given the option of collecting the documents before destruction.

14.3 Clinical Trial Insurance

Clinical trial insurance has been undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating study centers upon request.

14.4 Study Administrative Letters and Protocol Amendments

Astex Pharmaceuticals may issue Study Administrative Letters (1) to clarify certain statements or correct obvious errors/typos/inconsistencies in the study protocol, (2) to change the logistical or administrative aspects of the study, such as study personnel or contact information, or (3) to instruct investigators of DMC safety decisions for immediate implementation for safety reasons (Section 4.4).

For all other changes, Astex Pharmaceuticals will initiate any change to the protocol in a protocol amendment document. Astex Pharmaceuticals will submit the amendment together with a revised model ICF (if applicable), to regulatory authorities for approval before implementation, as required. The study center will submit the amendment to the IRB/IEC together with, if applicable, a revised model ICF. If the change in any way increases the risk to the subject, information on the increased risk must be provided to subjects already actively participating in the study, and they must read, understand and sign any revised ICF confirming willingness to remain in the study.

The investigator must obtain IRB/IEC approval before any protocol amendment can be implemented, except for administrative changes or changes necessary to eliminate an immediate risk to study subjects, as outlined above.

15.0 POLICY FOR PUBLICATION AND PRESENTATION OF DATA

The sponsor encourages the scientific publication of data from clinical research studies. However, investigators may not present or publish partial or complete study results individually without review by the sponsor. The principal investigators and the sponsor may propose appropriate scientific manuscripts or abstracts from the study data. The sponsor must review and comment on all proposed publications before submission for publication. The detailed procedures for the review of publications are set out in the clinical trial agreement entered into with the sponsor in connection with this study. These procedures are in place to ensure coordination of study data publication and adequate review of data for publication against the validated study database for accuracy. Names of all investigators and sponsor representatives responsible for designing the study and analyzing the results will be included in the publication(s).

Qualification of authorship will follow the requirements of the International Committee of Medical Journal Editors (www.icmje.org). In most cases, the principal investigators at the centers with the highest participation and accruals of eligible subjects and data in the study shall be listed as lead authors on manuscripts and reports of study results. The sponsor's medical monitor, study director and/or lead statistician may also be included in the list of authors. This custom can be adjusted upon mutual agreement of the authors and Astex Pharmaceuticals. In addition, other than clinical pharmacology studies in healthy volunteers or Phase 1 studies, all clinical studies must be registered with ClinicalTrials.gov.

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17.0 APPENDICES

APPENDIX 1: ECOG PERFORMANCE STATUS

Score	ECOG Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all 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
5	Dead

Source: ECOG Performance Status — http://www.ecog.org/general/perf_stat.html (accessed 25 March 2014)

APPENDIX 2: POOR-RISK CYTOGENETICS SPECIFICATION

Poor-risk cytogenetics are defined based on the NCCN Guidelines® (2014) as follows:

Risk Status Based on Cytogenetics[1]

Risk Status	Cytogenetics
Better-risk	inv(16)[2,3] or t(16;16)[2] t(8;21)[2] t(15;17)
Intermediate-risk	Normal cytogenetics +8 alone t(9;11) Other non-defined
Poor-risk	Complex (≥3 clonal chromosomal abnormalities) Monosomal karyotype -5, 5q-, -7, 7q- 11q23 - non t(9;11) inv(3), t(3;3) t(6;9) t(9;22)[4]

[1] The molecular abnormalities included in this table reflect those for which validated assays are available in standardized commercial laboratories. Given the rapidly evolving field, risk stratification should be modified based on continuous evaluation of research data. Other novel genetic mutations have been identified that may have prognostic significance.

[2] Other cytogenetic abnormalities in addition to these findings do not alter better risk status.

[3] Paschka P, Du J, Schlenk RF, et al. Secondary genetic lesions in acute myeloid leukemia with inv(16) or t(16;16): a study of the German-Austrian AML study group (AMLSG). Blood 2013;121:170-177.

[4] For Philadelphia+ AML t(9;22), manage as myeloid blast crisis in chronic myeloid leukemia, with addition of tyrosine kinase inhibitors.

Source: NCCN Guidelines: Acute Myeloid Leukemia. Version.2. 2014. NCCN.org.

APPENDIX 3: NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

Adverse events and/or adverse drug reactions will be graded according to the CTCAE version 4.03.

View the NCI CTCAE criteria electronically at the following web link:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40 (accessed 07 August 2014)

Click on "Common Terminology Criteria for Adverse Events (CTCAE) v4.0."

APPENDIX 4: EQ-5D-5L SAMPLE

The attached sample (in English) was downloaded from the EuroQol website:
http://www.euroqol.org/home.html
(accessed on 24 November 2014)

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

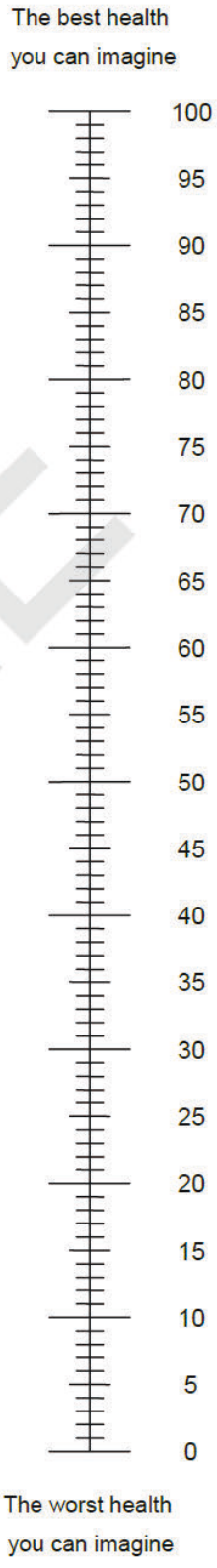
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX 5: SUMMARY OF CHANGES, AMENDMENT 1

Protocol: SGI-110-04

Amendment Date: 6 March 2015

Amendment 1 incorporates changes required by the Voluntary Harmonization Procedure (VHP) assessment of the protocol after clinical trial application in Europe.

Rationale for Amendment 1: VHP-required changes and sponsor administrative changes.

Summary of Changes:

1. Requirements were incorporated to specify use of 2 highly effective contraceptive measures during the study and for at least 3 months after completing treatment. Highly effective contraceptive measures are defined. Monthly pregnancy testing for women of child-bearing potential and pregnancy as a reason for discontinuation from study treatment were also incorporated **(Synopsis and Sections 5.2, 5.4.1, 9.5.1, 9.5.3.1, and 9.5.4.1)**.
2. Description is added that the use of decitabine, the active metabolite of SGI-110, alters fertility and is mutagenic. Recommendation is added to seek advice about preserving oocytes and sperm before the start of study treatment for men and women of child-bearing potential **(Section 8.0)**.
3. The timing of the screening pregnancy test was changed so that it must be done within 7 days of the start of study treatment **(Sections 9.5.1 and 9.5.2)**.
4. Prohibition of vaccination with live vaccines was added **(Section 7.5.2)**.
5. A statement was added that the sponsor will submit a protocol amendment and a revised model ICF to regulatory authorities for approval before implementation **(Section 14.4)**.
6. More information about life expectancy, harm, and quality of life for the TCs was added. Information on supportive care was also added **(Sections 1.2 and 16.0)**.
7. Two additional collection time-points for PK analysis were added (for a total of 4 sparse samples from 2 collection days) from SGI-110-treated subjects to enable more robust exposure-response analyses using a Population PK modeling approach **(Section 9.3)**.
8. A description was added to address alternative therapy upon progression or toxicity in the TC group **(Section 7.2)**.
9. A description of results from the 10-day regimen in previously untreated subjects with AML was added, based on preliminary data from Study SGI-110-01 Phase 2 Dose Expansion **(Section 2.2.3.2)**.
10. Rationale was added for the recommendation that SGI-110 study treatment should continue for at least 6 cycles **(Section 7.1.2)**.

11. Exclusion criterion #3 ("Known core binding factor (CBF) leukemia: t(8,21) or inv(16)") was deleted **(Synopsis and Section 5.2)**.

12. Exclusion criterion #7 was changed to include hypersensitivity to the TCs or any of their excipients **(Synopsis and Section 5.2)**.

13. Allowance of leukapheresis before randomization to reduce tumor burden, and prohibition of leukapheresis after randomization, was added **(Sections 7.4 and 7.5.1.3)**.

14. Summary of Product Characteristics (SPC) reference safety information was added, and existing reference to US prescribing information as examples was clarified **(Sections 7.2, 7.3.2, 8.0, and 16.0)**.

15. Clarification was added that Grade 3 and 4 cytopenias without an associated life-threatening clinical AE will not be considered SAEs in this study **(Section 10.1.2)**.

16. Clarification was added that "the last dose of study treatment" is synonymous with "discontinuation of treatment in the study" **(Sections 5.4.1 and 10.2)**.

17. Clarification that the study population eligibility describes adults with previously untreated AML who are "unfit to receive" or not considered candidates for intensive remission induction chemotherapy **(Synopsis and Sections 4.1 and 5.2)**.

18. TC decitabine and azacitidine dosing schedules were clarified to be daily **(Synopsis and Sections 1.4, 4.1, and 7.2)**.

19. Dose modification "based on Day 28 or later PB counts" was changed to "…Day 29…" to correspond with the schedule of events more closely **(Section 7.3.1)**.

20. The window for Day 1 assessments for Cycles ≥3 was widened from +6 days to +7 days **(Sections 9.5.1 and 9.5.4.1)**.

21. Clarification was added that the window for BM aspirate/biopsy is ±7 days around Day 1 of Cycles 3, 5, and 7 **(Section 9.5.1)**.

22. The sponsor drug safety contact number designation was corrected from phone to fax **(Title page and Section 10.3.1)**.

23. The address for the sponsor, Astex Pharmaceuticals, Inc., was updated **(Title page and Sponsor and Investigator Signature Page)**.

24. The model ICF was revised to correspond to these protocol modifications, as applicable.