CONFIDENTIAL

Clinical Study Protocol — SGI-110-01

A Phase 1-2, Dose Escalation, Multicenter Study of Two Subcutaneous Regimens of SGI-110, a DNA Hypomethylating Agent, in Subjects with Intermediate or High-Risk Myelodysplastic Syndromes (MDS) or Acute Myelogenous Leukemia (AML)

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Study Acknowledgement

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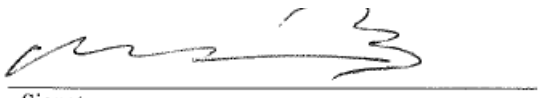
Amendment 1, 28 March 2011
Amendment 2, 05 April 2012
Amendment 3, 07 September 2012
Amendment 4, 15 March 2013
Amendment 5, 18 February 2014
Amendment 6, 09 May 2014

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

Mohammad Azab, MD
Medical Monitor Name (printed)


Signature

09 May 2014
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	Site Number
Institution Name	City, State

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

PROTOCOL APPROVAL PAGE

SGI-110-01: A Phase 1-2, Dose Escalation, Multicenter Study of Two Subcutaneous Regimens of SGI-110, a DNA Hypomethylating Agent, in Subjects with Intermediate or High-Risk Myelodysplastic Syndromes (MDS) or Acute Myelogenous Leukemia (AML)

Amendment 6, 09 May 2014

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PROTOCOL SUMMARY

Study Number and Title: SGI-110-01. A Phase 1-2, Dose Escalation, Multicenter Study of Two Subcutaneous Regimens of SGI-110, a DNA Hypomethylating Agent, in Subjects with Intermediate or High-Risk Myelodysplastic Syndromes (MDS) or Acute Myelogenous Leukemia (AML)

Clinical Phase: 1-2

Study Objective(s):

Primary

Dose Escalation Segment: Determine the overall safety profile, including dose limiting toxicities (DLTs) and determine the recommended Dose Expansion Segment regimen(s) by identifying the optimal biologically effective dose (BED) for each regimen, based on maximum global DNA hypomethylation and gene expression, OR based on the maximum tolerated dose (MTD) whichever occurs first during dose escalation.

Dose Expansion Segment: Evaluate the activity of SGI-110 as measured by overall remission rate.

Secondary

- Determine the pharmacokinetic (PK) profile of SGI-110 and decitabine.
- Remission duration, hematological improvement and transfusion independence rates.
- Determine epigenetic modulation in peripheral blood and bone marrow samples and whether any putative biomarkers (eg, cytogenetic or molecular) for SGI-110 response exists.

Study Design:

This study has two parts, a Dose Escalation Segment and a Dose Expansion Segment.

The study will be a multicenter, randomized, dose escalation study based on a 3 + 3 design within each regimen. Each dose cohort will have at least 3-6 subjects. Eligible subjects will receive 1 of 3 dosing regimens of SGI-110 with the following starting doses:

- Regimen 1: 3 mg/m^2/day subcutaneously on Days 1–5 of a 28-day course
- Regimen 2A (once weekly): 6 mg/m^2 subcutaneously Weekly x 3 on Days 1, 8, 15 of a 28-day course
- Regimen 2B (twice weekly): The proposed starting dose is 60 mg/m^2 twice weekly (this is the same total weekly dose from the last once weekly cohort that was safely tolerated) given subcutaneously for 3 weeks (Days 1, 4, 8, 11, 15, 18) of a 28-day course.

In the event that one of these starting doses is not tolerated, the next lower doses would be 1.5 mg/m^2/day in Regimen 1 and 3 mg/m^2 in Regimen 2A or to be determined by the Safety Review Committee (SRC) in Regimen 2B. Pharmacokinetics will be assessed in each regimen primarily during the Dose Escalation Segment, and in 10 relapsed/refractory AML subjects, 10 MDS subjects, and up to 20 treatment-naïve AML subjects treated in the Dose Expansion Segment. If a BED or MTD is reached in one regimen before the others, all subsequent subjects will be enrolled to the remaining regimen(s) until a BED or MTD is determined for each regimen. Randomization will resume for the Dose Expansion Segment of the protocol if the decision is made to expand dosing for more than one dose or dose regimen. The Dose Expansion Segment will commence upon identification of the BED or MTD for at least one regimen.

For the protection of study subjects in the Dose Escalation Segment, the SRC including the Principal Investigators at each study center, Astex Pharmaceutical's medical monitor, and study director will monitor, review and evaluate at least the 28-day safety data from a minimum of three subjects at each dose cohort before proceeding with the higher dose cohort.

Subsequent treatment courses could be administered as long as, in the judgment of the Investigator, the subject is still receiving benefit with acceptable toxicity. Subsequent courses may also be delayed or dose reduced based on the incidence of DLTs and recovery of hematological and other toxicity from previous courses.

Dose Escalation:

The active metabolite of SGI-110 is decitabine, an FDA-approved drug for the treatment of MDS. The reported mean maximum concentration (C_{max}) and area under the curve ($AUC_{0-\infty}$) for decitabine 20 mg/m^2 intravenous (IV) infusion over 1 hour daily for 5 days (n=11) was 147 ng/mL and 115 ng*h/mL, respectively [1]. Therefore, Astex Pharmaceuticals proposes the following dose escalation scheme for each regimen:

- 100% increments until 50% of the reported (for the approved dose) mean C_{max} of decitabine (74 ng/mL) OR 50% of the mean $AUC_{0-\infty}$ (58 ng*h/mL) is reached provided that no DLTs are observed.
- In the absence of DLTs, once a decitabine mean C_{max} of 74 ng/mL OR mean $AUC_{0-\infty}$ of 58 ng*h/mL is

reached, then the escalation will follow the sequence of (67%, 50%, 40%, and 33% increments thereafter). For Regimen 2B, escalation, if approved by SRC, will proceed only at 33% increments and only if it shows better hypomethylation levels than the once weekly regimen (Regimen 2A) and are similar to the daily regimen as determined by SRC review.

- If no DLTs occur in any subject, enrollment of subjects at the next dose level will occur.
- In the presence of one DLT in any subject, the cohort will have at least 6 subjects and then escalation may continue only as 33% increments or lower as decided by the SRC.
- In the presence of two or more DLTs in two or more subjects in one cohort, dose escalation will be stopped.

Intrasubject escalations will not be allowed; however, once an MTD or BED dose level is determined, a subject may be allowed to receive their subsequent cycles at that dose level at the Investigator's discretion. The MTD will be defined as the largest dose for which fewer than 33% of subjects experience a DLT during Course 1 of SGI-110 administration during the study. The BED will be defined as the smallest dose that achieves a maximum hypomethylation or gene expression in at least three successive dose levels. One or more dose or dose regimen may go forward to the Dose Expansion Segment of this study based on the results of the Dose Escalation Segment and review of all relevant data by the SRC.

Study Population: see details in Section 5.0

Inclusion Criteria

Subjects must fulfill all of the following criteria.

1. Subjects who are men or women, 18 years of age or older, with a confirmed diagnosis of IPSS intermediate-1, intermediate-2 or high-risk MDS including Chronic Myelomonocytic Leukemia (CMML), or AML.
   a. In the Dose Escalation Segment, subjects who are refractory, relapsed, or unresponsive to standard treatment will be the only ones allowed.
   b. In the Dose Expansion Segment, hypomethylating agent (HMA) treatment-naïve MDS subjects (including CMML), and intermediate-2 or high-risk MDS subjects (including CMML) relapsed or refractory to prior HMA treatment are allowed, and treatment-naïve AML subjects who are at least 65 years of age will be allowed if they also have at least one of the following criteria:
      1) AML secondary to MDS, chemotherapy, or radiation therapy,
      2) poor cytogenetics (see Section 5.0 for details),
      3) 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) which is unrelated to the leukemia.
      4) poor performance status, Eastern Cooperative Oncology Group (ECOG), of 2
      5) age ≥75 years
2. Subjects with ECOG performance status of 0 to 2.
3. Subjects with adequate organ function defined as:
   a. Hepatic: Total bilirubin ≤ 2 X upper limit of normal (ULN); aspartate transaminase (AST/SGOT) and alanine transaminase (ALT/SGPT) ≤ 2.5 X ULN.
   b. Renal: serum creatinine ≤ 1.5 X ULN.
4. Women of child-bearing potential (see details in Section 5.2) must not be pregnant or breastfeeding, must have a negative pregnancy test at Screening and all men must be practicing two medically acceptable methods of birth control. Men should not father a child while receiving treatment with SGI-110 and for 2 months following completion of treatment. Men with female partners of childbearing potential should use effective contraception during this time.
5. For subjects with prior allogeneic stem cell transplant, no evidence of active graft-versus host disease (GVHD) and must be ≥ 2 weeks off immunosuppressive therapy.
6. Subjects with no major surgery within 4 weeks of first dose of SGI-110.
7. Subjects with no chemotherapy within 2 weeks of first dose of SGI-110 (minimum of 6 weeks for nitrosoureas and 8 weeks for bone marrow transplantation) with the exception of hydroxyurea which will be allowed during Course 1 of treatment.
8. Subjects who sign an approved informed consent form for this study.
9. Subjects who are willing to comply with the protocol.

Exclusion Criteria

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

1. In the Dose Expansion Segment, which includes the 10-day regimen, subjects who have received 2 complete full dose cycles or more of a HMA decitabine or azacitidine (except for intermediate-2 or high-risk MDS subjects (including CMML) relapsed or refractory to prior HMA treatment).
2. Subjects with acute promyelocytic leukemia (M3 classification).
3. Subjects with prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for at least 3 years.
4. Subjects with life-threatening illnesses other than AML or MDS, uncontrolled medical conditions or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, or put the study outcomes at risk.
5. Subjects with uncontrolled or symptomatic arrhythmias, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification.
6. Subjects with symptomatic central nervous system (CNS) metastases or lesions requiring treatment.
7. Subjects who have received prior radiation therapy for extramedullary disease within 2 weeks of randomization.
8. Subjects with Grade ≥ 2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation.
9. Subjects with known history of human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV).
10. Subjects who have been treated with any investigational drug within 2 weeks of randomization.
11. Subjects who are being treated with systemic corticosteroids as treatment for their MDS or AML. Corticosteroids treatment for other conditions is allowed.
12. Subjects with uncontrolled active systemic infections.
13. Subjects who have hypersensitivity to decitabine, SGI-110, or SGI-110 excipients.
14. With the exception of treatment-naïve elderly AML subjects where certain co-morbidities are allowed per Inclusion Criterion #1b, subjects with uncontrolled CHF, CAD, COPD, or left ventricular ejection fraction (LVEF) of ≤ 50% are excluded.

Study Treatment (Investigational Product)

SGI-110 is supplied as a two-vial system. SGI-110 for Injection, 100 mg is a 5 mL glass vial containing lyophilized SGI-110 drug powder for reconstitution and subcutaneous (SQ) injection using the custom diluent supplied in a separate vial.

SGI-110 Diluent for Reconstitution, 3 mL is a 5 mL glass vial with 3 mL of custom diluent.

SGI-110 for injection is reconstituted using the diluent solution up to a maximum strength of 100 mg/mL. Subjects will be randomized to one of two treatment regimens: Regimen 1 (SQ dailyx5), and Regimen 2A (SQ once weeklyx3). Regimen 2B (SQ twice weekly on Days 1, 4, 8, 11, 15, 18) every 28 days at the Dose Escalation Segment was added in Amendment 2, and a 10-daily regimen at the Dose Expansion Segment was added in Amendment 3 (in refractory/relapsed AML subjects) and Amendment 5 (in treatment-naïve AML subjects).

Study Endpoints

Primary Endpoints

Dose Escalation Segment: Optimal BED as assessed by global DNA hypomethylation and gene-specific re-expression, or the MTD as assessed by Common Terminology Criteria for Adverse Events (CTCAE version 4.0) for each regimen.

Dose Expansion Segment: Overall remission rate as measured by the International Working Group (IWG) 2006 MDS Response Criteria [2] and 2003 AML Response Criteria [3].

Secondary Endpoints

- Incidence and severity grades of DLTs and other adverse events, and abnormal laboratory values
- C_{max}, C_{min}, AUC and other PK parameters of SGI-110 and decitabine
- Rates of hematologic improvement and duration of remission
- Time to AML or death (only for MDS subjects)
- Overall survival
- Incidence of blood and platelet transfusions

Study Procedures and Assessments:

Key Screening Procedures: Review of inclusion and exclusion criteria; review of medication(s) and medical history; physical examination; vital signs; ECOG performance status; 12-lead electrocardiogram (ECG); multiple-gated acquisition scan (MUGA) or echocardiogram (ECHO); bone marrow aspirate or biopsy and cytogenetics; hematology; chemistry; urinalysis; serum or urine pregnancy test; history of transfusion requirement. There is a 14-day screening period in this study.

Treatment and Follow-Up Procedures: All regimens have their visits on a weekly basis except for the 5-day and 10-day regimens where visits occur daily during the treatment days. Procedures and laboratory assessments include recording of adverse events (AEs), concomitant medications and transfusion requirements; symptom directed physical examination; weight and height; vital signs; ECOG performance status; 12-lead ECG; hematology; chemistry; pharmacokinetics, global DNA hypomethylation and gene-specific re-expression. There is a 30 (+ 5 day) follow-up period in this study.

Pharmacokinetics: Pharmacokinetics of both SGI-110 and decitabine will be assessed for each regimen during the Dose Escalation Segment, and in 10 relapsed/refractory AML subjects, 10 MDS subjects, and up to 20 treatment-naïve AML subjects treated in the Dose Expansion Segment.

Regimen 1 (QD x 5)

- Course 1, Day 1 and Day 5: pre-dose, 15 min, 30 min, 60 min, 90 min and 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, and 24 hr post-dose (pre-Day 2 for Day 1 samples)
- Course 1, Days 2–4: pre-dose

For Dose Expansion PK, the following time points are not required: Course 1, Day 1 24-hr post-dose; Course 1, Days 2-4; and Course 1, Day 5 pre-dose time points.

Regimen 2A (Weekly x 3)

- Course 1, Day 1 and Day 8: pre-dose, 15 min, 30 min, 60 min, 90 min and 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, and 24 hr post-dose

Regimen 2B (Days 1, 4, 8, 11, 15, 18 of a 28-day course)

Course 1, Day 1: pre-dose, 15 min, 30 min, 60 min, 90 min and 2 hr, 3 hr, 4 hr, 6 hr, and 8 hr post-dose

10-Day Regimen (Dose Expansion, treatment-naïve AML subjects)

- Course 1, Day 1: pre-dose, 15 min, 30 min, 60 min, 90 min and 2 hr, 3 hr, 4 hr, 6 hr, and 8 hr post-dose
- Course 1, Day 12: pre-dose and 2 hr (± 30 min) post-dose

Global DNA Hypomethylation and Gene-Specific Re-expression: Collection of blood samples pre-dose Day 1, and pre-dose each day at Days 8, 15, and 22 during Course 1 and pre-dose at Day 1 of Course 2. A buccal swab will be taken before the first dose of study drug.

The following DNA methylation and gene-specific re-expression markers will be evaluated:

- Gene specific expression ($p15^{INK4b}$)
- Global DNA hypomethylation in LINE-1 sequence
- Other gene expression markers: miRNA-124a, ataxia telangiectasia mutated (ATM)
- Additional biomarkers as they become known

Sample Size and Statistical Analyses:

Statistical Considerations:

Sample Size Calculation: No formal statistical tests of hypotheses will be performed comparing SGI-110 to control treatment, as is characteristic in Phase 1 trials. The number of subjects enrolled during the Dose Escalation Segment of the study is based on response (DNA hypomethylation, gene expression or occurrence of DLTs) to SGI-110. At the recommended Dose Expansion Segment dose(s) and schedule(s), a minimum of 30 subjects will be enrolled in each of the following 6 subgroups: 1) HMA treatment-naïve MDS (including CMML); 2) relapsed/refractory intermediate-2 or high-risk MDS (including CMML); 3) relapsed/refractory AML treated with the 5-day regimen; 4) relapsed/refractory AML treated with the 10-day regimen; 5) treatment-naïve elderly AML subjects treated with the 5-day regimen; and 6) treatment-naïve elderly AML subjects treated with the 10-day regimen. The sample size of 30 subjects in each subgroup was selected so that if no responses were observed it will be concluded, with 95% confidence, that the response rate in that subgroup is <10% and therefore not worthy of further development. The SRC for a particular subgroup, where the most number of responses are observed, may increase the number of subjects up to 50 subjects per subgroup to have a better assessment of efficacy in that subgroup.

Safety: Within each dosing regimen, SGI-110 MTD will be defined as the largest dose for which fewer than 33% of subjects experience a DLT during the first course of administration. Safety will be assessed by subject

reported and Investigator observed AEs along with physical examination, clinical laboratory tests (hematology, chemistries, and urinalysis), and serial ECGs. Safety variables will be tabulated and presented for all subjects who receive any amount of SGI-110. Exposure to SGI-110 and reasons for discontinuation will be tabulated. Summarization will focus on rates for the following; rates of treatment emergent AEs by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term; by CTC grades, and reasons for discontinuation of SGI-110.

Efficacy: Within each regimen, assessments of hypomethylation will be plotted against SGI-110 dose to determine the dose level at which hypomethylation plateaus, where plateau is defined as absence of meaningful increase in hypomethylation over three consecutive dose levels. If a plateau in hypomethylation is observed before reaching the MTD, then the minimum BED will be defined as the lowest SGI-110 dose level of the plateau. Response rates and 95% confidence intervals will be estimated for the Dose Expansion segment. Overall survival is defined as the number of days from the day the subject received the first dose of SGI-110 to the date of death (regardless of cause). For subjects entering the study with MDS, time to AML or death is the number of days from the day the subject received the first dose of SGI-110 to the date of death or the date of MDS progression to AML defined by ≥ 20% blasts in bone marrow or peripheral blood.

Pharmacokinetics: PK parameters will be derived for each subject using non-compartmental approach. Descriptive statistics including mean, SD, median and range for PK parameters for SGI-110 and decitabine will be summarized by cohort and regimen. PK dose proportionality will be tested using linear regression between dose and dose-adjusted parameter estimates; correlation of PK to PD will be assessed.

Study Duration:

It is estimated that the Dose Escalation Segment will take approximately 12-18 months to complete enrollment for an estimate of 4 to 8 cohorts per regimen to determine the optimal BED or MTD. The Dose Expansion Segment is expected to have an additional 12-18 month enrollment period.

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ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
ALT	Alanine transaminase also called serum glutamic pyruvic transaminase (SGPT)
AML	Acute myelogenous leukemia
ANC	Absolute neutrophil count
AST	Aspartate transaminase also called serum glutamic oxaloacetic transaminase (SGOT)
ATM	Ataxia telangiectasia mutated (protein)
AUC	Area under the curve
BED	Biologically effective dose
BSA	Body surface area
CAD	Coronary artery disease
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CMML	Chronic myelomonocytic leukemia
CNS	Central nervous system
C_{max}	Maximum concentration
COPD	Chronic obstructive pulmonary disease
CR	Complete remission
CRF	Case report form
CRi	Complete remission with incomplete blood count recovery
CRp	Complete remission with incomplete platelet recovery
CTA	Cancer testis antigens
CT scan	Computed tomography scan
CTCAE	Common Terminology Criteria for Adverse Events (http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf)
CV	Coefficient of variation
DLCO	Diffusing capacity of the lung for carbon monoxide
DLT	Dose-limiting toxicity
DNMT	DNA methyltransferase
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECHO	Echocardiogram
FAB	French-American-British
FEV1	Forced expiratory volume in the first second
FDA	Food and Drug Administration
FOB	Functional observational battery
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVHD	Graft versus host disease
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
hERG	Human ether-a-go-go-related gene
HI	Hematological improvement
HI-E	Hematological improvement – erythroid response
HI-P	Hematological improvement – platelet response

HI-N	Hematological improvement – neutrophil response
HIV	Human Immunodeficiency Virus
HNSTD	Highest non-severely toxic dose
HMA	Hypomethylating agent
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IPSS	International Prognostic Scoring System
IRB	Institutional Review Board
IUD	Intrauterine device
IV	Intravenous
IWG	International Working Group
LINE-1	Long interspersed nucleotide element-1
LVEF	Left ventricular ejection fraction
mCR	Marrow complete response
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
MUGA scan	Multiple-gated acquisition scan
NOAEL	No-observed-adverse-effect-level
NOEL	No-observed-effect-level
PO	By mouth (per os)
PR	Partial remission
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
QT	QT interval
QTc	Heart rate corrected interval
RBC	Red blood cells
SAE	Serious adverse event
SCT	Stem cell transplant
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SRC	Safety Review Committee
STD	Severely toxic dose
SQ	Subcutaneous
TERM	Termination
ULN	Upper limit of normal

1.0 INTRODUCTION AND BACKGROUND

The study will be conducted in compliance with the protocol, International Conference on Harmonisation (ICH) good clinical practice (GCP) guidelines, and the applicable regulatory requirements.

1.1 Background of Myelodysplastic Syndromes (MDS)

MDS is a hematologic disorder of adults, with an estimated incidence (age adjusted) of 4 cases per 100,000 people annually in the United States (Ref: http://www.leukemia-lymphoma.org//all_page.adp?item_id=522246; accessed 12 May 2010). MDS is characterized by ineffective hematopoiesis with progressive cytopenias and a variable risk of transformation to acute myeloid leukemia (AML) [4]. For patients with intermediate-2 (Int-2) or high-risk disease as defined by the International Prognostic Scoring System (IPSS), the median overall survival (OS) is 1.2 years or 0.4 years, respectively, and these patients have a high risk of transformation to AML [5]. The goal of therapy for these patients is, therefore, to modify the natural history of the disease and extend the survival and time to AML transformation. With the exception of allogeneic stem cell transplantation (SCT), for which most patients are unsuitable due to their age, there is currently no curative treatment for MDS, and older patients, who comprise the majority of those affected, generally receive supportive care, low dose chemotherapy, or investigational treatments. Development of specific MDS treatments has been challenging not only by the limitations of treatment tolerance, but also by the frequent unfavorable biological features of the malignant clone. These include adverse cytogenetics, limited normal stem cell reserve, and higher levels of multidrug resistance. The recent development of non-intensive epigenetic therapy with azanucleosides has been driven by the goal of "re-programming" growth and differentiation, rather than eradication by cytotoxic effects, of the abnormal cells. The association between MDS and AML has long been recognized.

The French-American-British (FAB) classification system distinguishes MDS from AML on the basis of bone marrow blast percentage. According to this system, patients with ≥ 30% blasts are defined as having AML with as much as 70% of MDS patients will develop AML over a period of months to a few years. Factors influencing the risk of and time to development of AML in MDS include the percentage of blasts in the marrow, the presence of clonal cytogenetic abnormalities and multiple cytopenias. Survival among MDS patients progressing to AML is uniformly poor and seldom exceeds a few months.

1.2 Background of Acute Myeloid Leukemia (AML)

Acute myeloid leukemia is the most common leukemia diagnosed in adults. In the United States, an estimated 12,810 people will be newly diagnosed with AML in 2009 and approximately 9,000 will die from their disease (American Cancer Society website: http://www.cancer.org/docroot/CRI/content/CRI_2_4_1x_What_Are_the_Key_Statistics_About

_Acute_Myeloid_Leukemia_AML.asp?sitearea; accessed 25 March 2010). The 5-year survival rate is 19%. As the population in the United States ages, there appears to be an increasing incidence of AML in the patients over age 65 years.

AML can be divided between de novo and secondary disease [6] [7]. Secondary causes for AML range from previous myelodysplasias to long-term treatment consequences of certain chemotherapeutic agents to exposure to environmental hazards (ie, benzene). The disease is characterized by an inhibition of cellular differentiation of the myeloid precursor cells of white and red blood cells and platelets. This results in a massive accumulation of immature or blast cells in the bone marrow and other organs. Median survival for untreated AML is less than 3 months. A diagnosis of AML necessitates a rapid assessment and planning. The goal of therapy is to achieve as quickly as possible a complete and prolonged remission, perhaps resulting in a cure. Therapy for good risk patients is generally an induction therapy with a single or combination of chemotherapeutic agents, usually high-dose or standard dose cytarabine with or without an anthracycline and/or mitoxantrone and/or etoposide [8]. If a complete remission is achieved, a bone marrow transplant or consolidation therapy is undertaken. Patients who are refractory to this therapy or who relapse within 1 year or who are considered high risk for intensive chemotherapy (one or more of the following: ≥ 65 years, not having one of the good-risk cytogenetic abnormalities, and are unable or unwilling to undergo intensive chemotherapy) have few treatment options and as a result the prognosis for these patients is particularly poor. Median survival for these patients is 6 months or less [8].

The incidence of AML increases with age. Current chemotherapeutic options for elderly AML provide minimal chance for durable remission, with significant toxicity. Moreover, elderly AML subjects are rarely candidates for potentially curative allogenic stem cell transplantation. Standard chemotherapy generally achieves a complete remission rate of 45-60%, yet most patients relapse, and median survival is approximately 9 months [9] [10] [11]. Even among the relatively healthy patients, induction mortality in the elderly is 10-20% [10] [12] [13]. Consequently, many older AML patients are not offered or choose to decline traditional intensive chemotherapy and receive either investigational treatment, low dose cytarabine, or supportive care only. More effective therapies to provide durable remissions in a significant proportion of patients and less toxic therapies, which could be offered to more patients, are needed for the treatment of AML in the elderly.

1.3 DNA Methylation Inhibitors and Decitabine

DNA methylation is a reversible epigenetic process [14]. Aberrant DNA hypermethylation is a dominant mechanism in MDS progression to AML. The only approved way to target DNA methylation is to inhibit the DNA methyl transferase (DNMT) enzymes. There are currently two FDA-approved DNMT inhibitors for the treatment of MDS; these are the nucleoside analogs azacitidine and 2'-deoxy-5-azacytidine, or decitabine. These drugs reverse aberrant hypermethylation. They inhibit DNA methylation *in vitro* when present during DNA replication.

Once incorporated into the DNA, in place of cytosines, azacitidine and decitabine form irreversible adducts with DNMT, permanently inactivating the enzyme. This leads to the depletion of DNMT inside the cell [14]. When DNA synthesis occurs in absence of DNMT, the cytosine residues in daughter DNA strands do not become methylated [15]. Thus, the previously methylated genes can be re-expressed in daughter cells and can potentially promote normal cellular differentiation, senescence, or apoptosis [15].

Since 2000, four studies have investigated the effects of decitabine monotherapy in slightly different populations and using slightly different administration schedules [16] [17] [18] [19]. Two of these studies used the 3-day, 9-dose regimens requiring inpatient hospitalization, and two used 5-10 day decitabine regimens intended for administrations as an outpatient.

The US Phase 3 registration study compared decitabine (15 mg/m^2 continuous 3 hour intravenous [IV] infusion every 8 hours for 3 days repeated every 6 weeks) with supportive care in 170 patients with a confirmed diagnosis of de novo or secondary MDS. Most patients (69%) had int-2 or high-risk disease as defined by the IPSS criteria, and were red blood cell transfusion dependent (71%) [16]. Patients treated with decitabine had a 9% CR rate and a 30% overall improvement rate (CR + partial remission + hematologic improvement [HI]) using the International Working Group (IWG) 2000 criteria [20] compared to no CRs and a 7% overall improvement rate for patients who received supportive care. The median duration of response to decitabine treatment was 10.3 months (range, 4.1-13.9 months). Neutropenia (87%), thrombocytopenia (85%), anemia (12%), febrile neutropenia (23%), and leucopenia (22%) were the most commonly observed hematological adverse events.

Kantarjian *et al*. [17] compared 3 decitabine schedules administered in the outpatient setting. In this single-institution study, 95 patients were randomized to receive 20 mg/m^2/day IV for 5 days, 20 mg/m^2/day subcutaneously for 5 days, or 10 mg/m^2/day IV for 10 days repeated every 4 weeks. Most patients included in the study were aged ≥ 60 years (71%), and 66% of patients had IPSS int-2 or high-risk disease. Overall, patients received a median of > 7 treatment courses (range, 1–18). The 5-day IV schedule yielded the highest CR rate compared with the 5-day subcutaneous schedule and 10-day IV schedule (39% vs. 21% and 24%, respectively). Overall, 69 patients (73%) showed a response (CR + PR + HI). The 10-day treatment course was associated with a higher incidence of myelosupression and hospitalization compared with the other 2 treatment regimens. The median survival reported in this study was 19 months.

To follow-up on regimen comparisons studied by Kantarjian *et al.*, the single-arm North American multicenter study assessed the efficacy and safety of decitabine administered on a schedule of 20 mg/m^2/day IV for 5 days, every 4 weeks in patients with MDS [19]. Patients received a median of 5 courses of decitabine treatment (range, 0-17). By IWG criteria [2], there were 17% CRs, 15% bone marrow CRs, and 18% HI, for an overall improvement rate of 51%. The overall remission rate by IWG 2000 criteria was 43%. A third of the 66 patients who were red blood cell transfusion dependent at baseline became red blood cell transfusion independent

during the study. Cytopenias were the most common adverse events, but was less pronounced than the 15 mg/m^2 every 8 hour IV infusion for 3 days, with 31% of the patients developing neutropenia, 18% thrombocytopenia, > 14% febrile neutropenia, and 12% anemia.

In conclusion, several studies established the efficacy of decitabine in MDS subjects with 2 approved regimens. The 20 mg/m^2 per day administered intravenously for 5 days appear to be better tolerated with less myelosuppression.

1.4 SGI-110

Further information is available in the Investigator Brochure.

1.4.1 General Information

The active metabolite of SGI-110 (2'-deoxy-5-azacytidylyl-(3'→5')-2'-deoxyguanosine sodium salt), a dinucleotide, is decitabine. SGI-110 is resistant to modification by cytidine deaminase, a common pathway of decitabine metabolism and deactivation [21]. The molecular weight of SGI-110 and decitabine are 580 Da and 228 Da, respectively. Therefore, the molar equivalent dose of 1 mg of decitabine is approximately 2.5 mg of SGI-110. SGI-110's activity was demonstrated with the same preclinical pharmacodynamic assays used to demonstrate decitabine's efficacy eg, re-expression of p15, p16, and MLH1 and induction of fetal hemoglobin, *in vivo*. In xenograft studies, SGI-110 demonstrates promising preclinical activity in both hematologic and solid tumors.

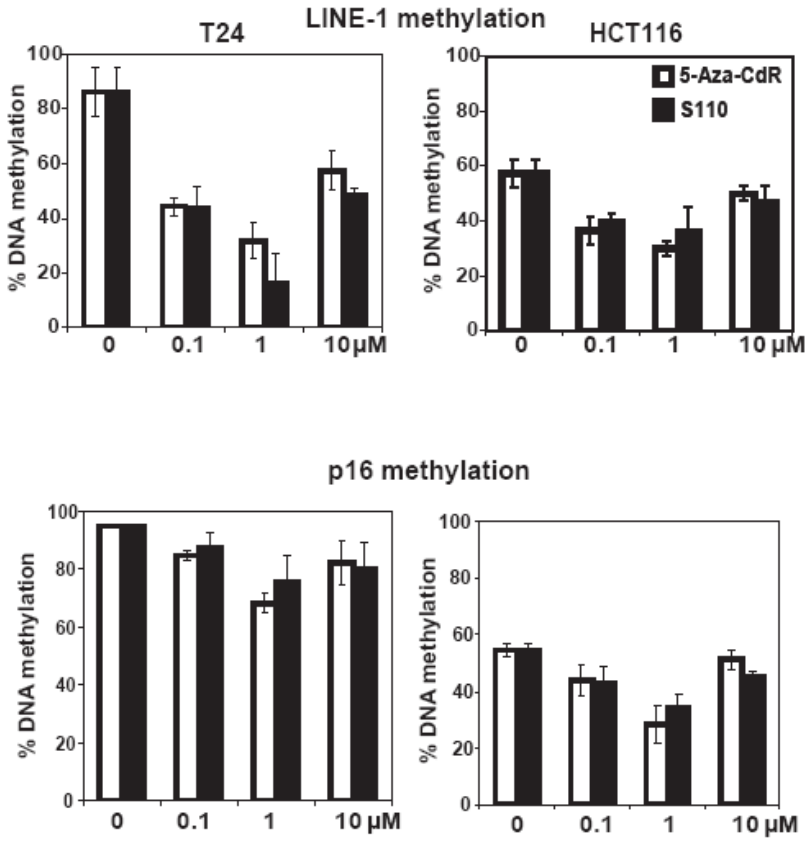
In vitro evidence suggests that SGI-110 has a longer half-life than decitabine in the presence of cytidine deaminase. Exploratory preclinical studies demonstrate that unlike decitabine, SGI-110 can suppress the polycomb repressor complex 2 which is involved in silencing tumor suppressor genes. These promising observations suggest that SGI-110 has improved pharmaceutical properties and biological activities that expand on decitabine's current clinical utility. SGI-110 has shown to be better tolerated in mice than decitabine and is as effective *in vivo* in inducing p16 expression, reducing DNA methylation at the p16 promotor region, and retarding EJ6 human bladder cancer tumor growth in athymic mice [22].

1.5 Summary of Nonclinical Data

1.5.1 *In Vitro* Pharmacology

The ability of SGI-110 to change global methylation status was tested by determining the methylation level of long interspersed nucleotide element-1 (LINE-1) and p16 sequences (Figure 1). Repetitive DNA elements, such as LINE-1 retrotransposable elements, serve as useful markers of genome-wide methylation changes and have previously been shown to be demethylated upon treatment with SGI-110 or decitabine (5-Aza-CdR).

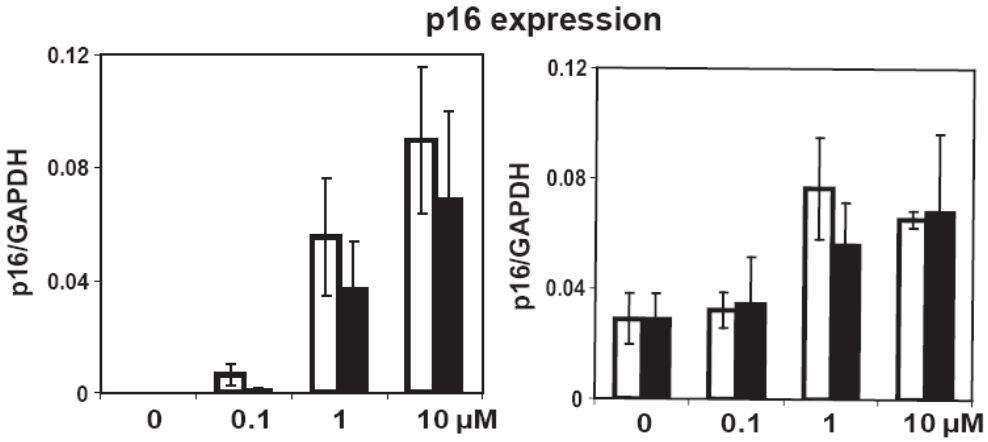
Figure 1: Effects of SGI-110 (filled bars) and Decitabine (open bars) on LINE-1 and p16 Gene Methylation Levels in T-24 and HCT116 Cell Lines



In both T-24 and HCT116 cells, the decrease in the level of methylation was dose-dependent and comparable for decitabine and SGI-110 after 0.1 µM and 1 µM treatment (Figure 1). In the figure noted above and any subsequent places in this document, S110 is the same as SGI-110. At 10 µM concentrations, only a small decrease in methylation was noted, probably due to side effects of high drug concentrations. In fact, 10 µM treatment may be too cytotoxic for effective demethylation to take place as the plating efficiency of T-24 cells indicates. It is well-established that the cytotoxic dose of these demethylating agents is not ideal for optimal epigenetic therapy, since these drugs inhibit DNA methylation best at low doses in cell lines as well as in the clinic.

Next, the changes in a methylation-silenced tumor suppressor gene, p16 were assayed in both cancer cell lines.

Figure 2: Effects of SGI-110 (filled bars) and Decitabine (open bars) on p16 Gene: Expression Levels in T-24 (left) and HCT116 (right) Cells



As shown in Figure 2, untreated T-24 bladder carcinoma cells do not express p16, and dose-dependent increases in p16 expression were observed after 6 days of continuous treatment with decitabine or SGI-110. After HCT116 colorectal carcinoma cells were treated for six days, a dose dependent increase in p16 expression was observed with both SGI-110 and decitabine.

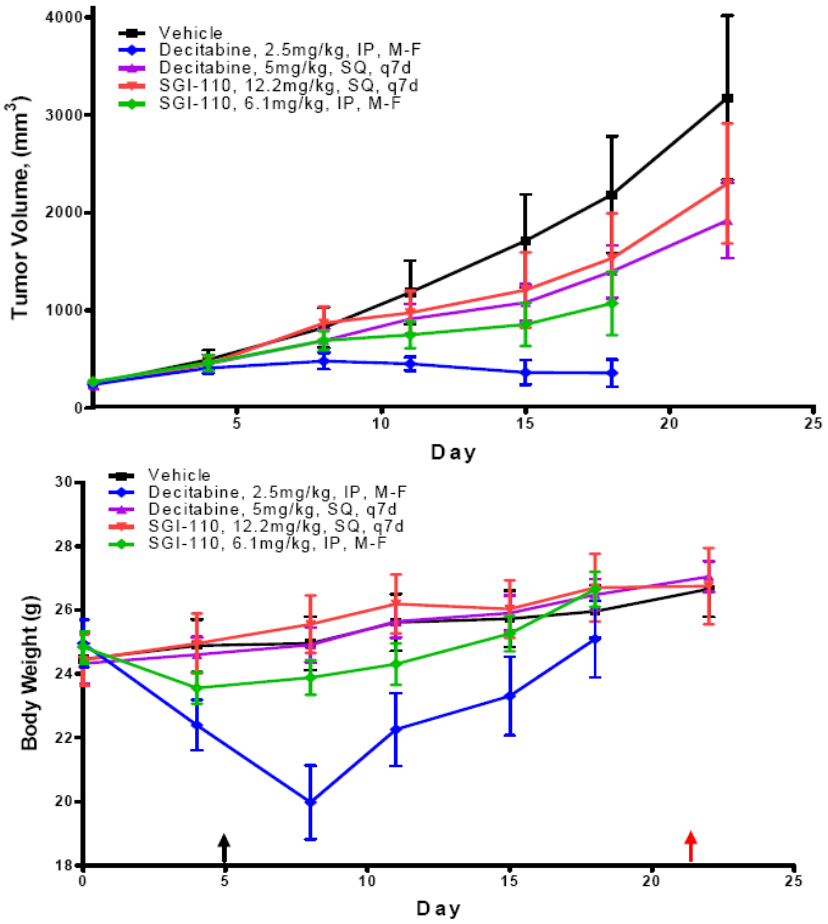
1.5.2 *In Vivo* Pharmacology

The efficacy and safety of SGI-110 was evaluated in several solid tumor models and HL-60 promyelocytic leukemia in comparison to equivalent doses of decitabine (Astex Pharmaceuticals, Inc., data on file). Female nu/nu mice were implanted subcutaneously with HL-60 cells. Animals with exponentially growing tumors were randomized into 5 groups of 8 animals each to include vehicle, decitabine 5 mg/kg administered subcutaneously every 7 days and 2.5 mg/kg administered intraperitoneally Monday to Friday. Equivalent doses and schedules of SGI-110 12.2 mg/kg and 6.1 mg/kg, respectively, were administered subcutaneously for comparison. Results from this study are shown in Table 1 and Figure 3. Both SGI-110 and decitabine demonstrated equivalent antiproliferative activity when administered subcutaneously. When dosed intraperitoneally, decitabine seemed to have a greater effect but at the expense of higher toxicity as evidenced by more weight loss and death of 1 animal in the decitabine group.

Table 1: Anti-tumor and Toxic Effect of SGI-110 or Decitabine in HL-60 Promyelocytic Leukemia

Group	Compound	Dose	Route, Schedule	% T/C	Tumor Growth Rate (mm3/day)	% Survival
1	Vehicle	-	IP, M-F	100	132.96	100
2	Decitabine	5 mg/kg	SQ, Q7D	57.53 (day 22)	76.50 (day 22)	100
3	Decitabine	2.5 mg/kg	IP, M-F	6.01 (day 18)	6.45 (day 18)	87.5
4	SGI-110	12.2 mg/kg	SQ, Q7D	69.90 (day 22)	92.94 (day 22)	100
5	SGI-110	6.1 mg/kg	IP, M-F	41.45 (day 18)	44.55 (day 18)	100

Figure 3: SGI-110 and Decitabine Activity and Body Weight Loss in HL-60 Promyelocytic Leukemia



1.5.3 General Safety (Cardiac, CNS, and Respiratory)

In a non-good laboratory practice (GLP) study, SGI-110 was tested to examine the *in vitro* effects on the human ether-a-go-go related gene (hERG) potassium channel current. Whole cell patch clamp recordings were made on human embryonic kidney (HEK293) cells that were stably

transfected with hERG cDNA. SGI-110 was tested at 10 μM and 300 μM. SGI-110 inhibited hERG current by 1.4 ± 0.3% (mean ± SEM) at 10 μM and by 1.0 ± 1.3% 300 μM. The half maximal inhibitory concentration (IC_{50}) for the inhibitory effect of SGI-110 on hERG current was not calculated but was estimated to be greater than 300 μM.

The potential neurobehavioral toxicity of SGI-110 was studied after a single subcutaneous dose of SGI-110 (0, 5, 10, and 20 mg/kg) in 2 repeat dose GLP toxicology studies in rats. Functional Observational Battery (FOB) evaluations were conducted on 10 main study animals/group pre-dose (Day -1) and 1 hour post-dose on Day 1 of the study [23] [24]. There were no SGI-110 related changes in any of the FOB measurements in either study. The no-observed-adverse-effect level (NOAEL) of SGI-110 on neurobehavioral function is 30 mg/kg.

The potential effects of SGI-110 on respiratory function were studied in a GLP study in rats. Pulmonary function (respiratory rate, tidal volume, and minute volume) were monitored continuously on 8 animals/sex/group for at least 1 hour pre-dose and at least 4 hours post-dose. Test article or vehicle was administered to all groups via a single subcutaneous injection (0, 15, 30, and 60 mg/kg) SGI-110 did not produce mortality and had no effect on clinical signs, respiratory rate, tidal volume, and minute volume. With respect to the basic pulmonary endpoints evaluated in this study, a no-observed-effect-level (NOEL) of at least 60 mg/kg has been established for SGI-110.

1.5.4 Genotoxicity and Mutagenicity

No studies were performed to evaluate the genotoxicity and mutagencity potential of SGI-110.

1.5.5 Teratogenicity

As decitabine has known teratogenic effects, and as decitabine is the active metabolite of SGI-110, SGI-110 is presumed to be teratogenic as well.

1.5.6 Single and Repeat Dose Early Safety and Pharmacokinetics Studies

Single and repeat dose studies were conducted in mice, rats, monkeys and rabbits to evaluate the initial safety and pharmacokinetic parameters of SGI-110 as a sodium salt using various routes of administration including intravenous bolus, oral and subcutaneous. Once in a biological system, SGI-110 is cleaved by phosphodiesterases to form decitabine and the rate of this process is species-dependent. Pharmacokinetics of both SGI-110 and decitabine were evaluated after SGI-110 administration. Decitabine appeared to form faster and to a higher degree in mice, rats and rabbits with much lower levels of SGI-110 detected in plasma from these species. In monkeys, in contrast, the formation of decitabine appeared to be slower and levels of SGI-110 persisted for longer and at higher levels compared to mice, rats or rabbits. When administered via the subcutaneous route, the relative bioavailability appeared to be high at close to 100%.

In the pivotal 5-day GLP repeat-dose toxicity study in rats using subcutaneous bolus injection daily for 5 consecutive days at up to 20 mg/kg/d dosage of SGI-110, the severely toxic dose in 10% of the animals (STD_{10}) was determined to be higher than 20 mg/kg/d for 5 days. After 20 mg/kg/d for 5 days, SGI-110 administered subcutaneously, the SGI-110 C_{max} and AUC_{0-t} on Day 1 were 214 ng/mL and 215 ng*h/mL, and on Day 5 were 637 ng/mL and 486 ng*h/mL, respectively. The decitabine C_{max} and AUC_{0-t} on Day 1 were 5,372 ng/mL and 39,905 ng*h/mL and on Day 5 were 5,443 ng/mL and 40,724 ng*h/mL, respectively.

In the pivotal 5-day GLP repeat-dose toxicity study in rabbits using subcutaneous bolus injection daily for 5 consecutive days at dosages of 1.5, 3.5, and 7.0 mg/kg of SGI-110, the HNSTD was 1.5 mg/kg/d for 5 days (see Section 2.2 for further discussion). After 1.5 mg/kg/d for 5 days, SGI-110 administered subcutaneously, the SGI-110 C_{max} and AUC_{0-t} on Day 1 were 8.36 ng/mL and 5.58 ng*h/mL and on Day 5 were 7.45 ng/mL and 8.3 ng*h/mL, respectively. In contrast, decitabine C_{max} and AUC_{0-t} on Day 1 were 257 ng/mL and 996 ng*h/mL, and on Day 5 the levels were 247 ng/mL and 1,128 ng*h/mL, respectively.

Similar to the 5-day regimen, rabbits were also the most sensitive species in the weekly regimen. In the pivotal 3-week GLP repeat-dose toxicity study in rabbits using subcutaneous bolus injection weekly for 3 consecutive weeks at dosages of 0.5, 1.5, and 3.0 mg/kg of SGI-110, the HNSTD was 1.5 mg/kg weeklyx3 (see Section 2.2 for further discussion). After 1.5 mg/kg SGI-110 administered subcutaneously on Days 1,8, and 15, the SGI-110 C_{max} and AUC_{last} on Day 1 were 1.9 ng/mL and 0.475 ng*h/mL and on Day 15 were 3.84 ng/mL and 0.96 ng*h/mL, respectively. Decitabine C_{max} and AUC_{last} on Day 1 were 187 ng/mL and 850 ng*h/mL, and on Day 15 the levels were 191 ng/mL and 876 ng*h/mL, respectively.

In a 3-week non-GLP subcutaneous dose toxicity study in non-naïve Cynomolgus monkeys at a weekly dosage of 3 mg/kg for 3 weeks, plasma SGI-110 C_{max} and AUC_{last} after the first dose were 184 ng/mL and 356 ng*h/mL and after the third dose were 181 ng/mL and 592 ng*h/mL, respectively. Decitabine C_{max} and AUC_{last} after the first dose were 33.4 ng/mL and 116 ng*h/mL, and after the third dose the levels were 27.6 ng/mL and 99.4 ng*h/mL, respectively. The dose of 3 mg/kg weekly for 3 weeks was well tolerated in monkeys (see Section 2.2 for further discussion).

1.5.7 *In vivo* Nonclinical Biology - Pharmacodynamics

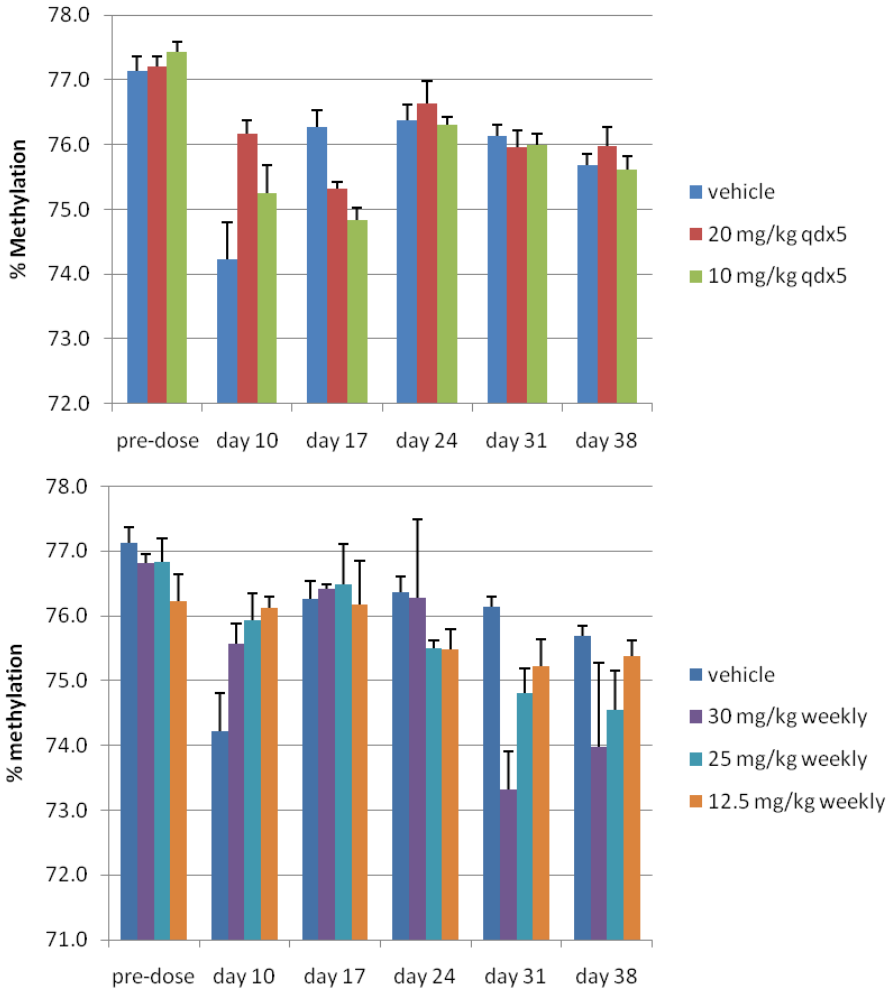
1.5.7.1 Effect of Subcutaneous Delivery of SGI-110 on Methylation of LINE-1 Rat DNA Sequence

Pharmacodynamic effects of SGI-110 on global DNA methylation were evaluated after subcutaneous delivery of the compound formulated in 65% propylene glycol, 25% glycerol, 10% ethanol. SGI-110 was administered daily for 5 days at 10 and 20 mg/kg and weekly for 4 weeks at 12.5, 25 and 30 mg/kg. Each treatment group included 6 rats and blood samples were collected from each animal at Day 10, 17, 24, 31 and 38. Data presented in Figure 4 present the average

between the mean % methylation of the 10 CpG sites for each treatment group and time point evaluated.

All doses and schedules were well tolerated. Changes in LINE-1 DNA methylation after subcutaneous (SQ) SGI-110 daily x 5 were not evident already at Day 10 (the earliest time point evaluated). Changes in LINE-1 DNA methylation after SQ SGI-110 weekly x 4 were evident during the first recovery week (Day 31) and were dose-dependent. The change in methylation observed on Day 31 in the group treated weekly with 30 mg/kg SGI-110 was about 5% lower than the methylation level observed in vehicle treated rats.

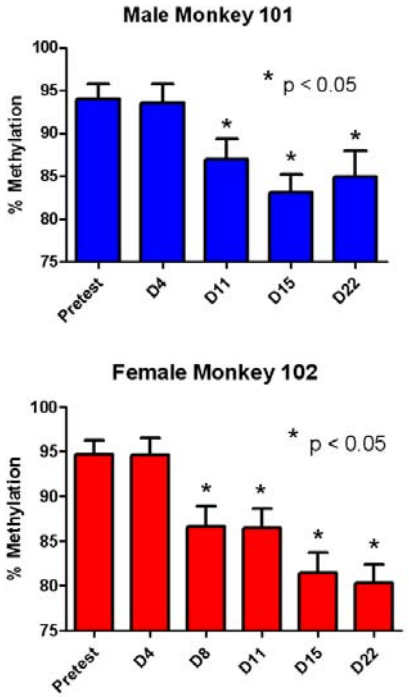
Figure 4: Percent Methylation of LINE-1 Rat Sequence After Daily or Weekly SQ Treatment with SGI-110



1.5.7.2 Effect of Subcutaneous Delivery of SGI-110 on Methylation of LINE-1 Monkey DNA Sequence

Pharmacodynamic effects of SGI-110 on global DNA methylation were also evaluated after subcutaneous delivery of the compound to Cynomolgus monkeys. SGI-110 was administered weekly (Day 1, 8 and 15) for 3 weeks at 3 mg/kg. Two animals (1 male and 1 female) were treated in this experiment and blood samples were collected pre-dose and on Day 4, 8, 11, 15 and 22 (prior to dosing on Days 8 and 15). Genomic DNA was subjected to bisulfite modification and analyzed by pyrosequencing of the monkey LINE-1 sequence. A total of 4 different CpG sites were analyzed within a 107 bp amplicon. Changes in LINE-1 DNA methylation after SQ SGI-110 weekly x 3 became evident at Day 8 in the female and Day 11 in the male and were maintained at least until Day 22 (the latest time point evaluated). The observed LINE-1 methylation decrease was significantly different from the methylation level observed in the blood sample obtained from the same animal before administration of the first dose (Figure 5).

Figure 5: Percent Methylation of LINE-1 Monkey Sequence after Weekly SQ Treatment with SGI-110



1.6 Summary of Clinical Data

For the most updated clinical data, please refer to the most recent Investigators' Brochure.

Early data from the Dose Escalation Segment are available. Data collection and cleaning are still ongoing so these data are still considered preliminary. Seventy-eight (78) patients (64 AML, 14 MDS) were enrolled in the Dose Escalation Segment: 44 patients in the daily x 5 regimen and 34 in the weekly x 3 regimen.

The PK profile demonstrated efficient conversion of SGI-110 to decitabine as predicted from the SGI-110 rational design, resulting in longer decitabine exposure window (beyond 8 hours) compared to Dacogen IV (3-4 hours). At SGI-110 dose range of 60-125 mg/m^2, observed mean decitabine AUCs (88-231 ng*hr/mL) reach or exceed the therapeutic range seen with 20 mg/m^2 Dacogen IV (115 ng*hr/mL) while achieving only a small fraction of the C_{max} (26-64 ng/mL vs 146 ng/mL for Dacogen IV). The effective half-life for decitabine after subcutaneous SGI-110 injection appeared to be prolonged (up to 4-fold or ~2.4 hours) compared to Dacogen IV (0.58 hrs). Decitabine exposures (AUC) increased in a dose-proportional manner regardless of the regimen and no accumulation was observed.

Dose-related LINE-1 hypomethylation was observed in patients treated with the daily regimen between 18 and 60 mg/m^2; a plateau in maximum average hypomethylation (~25%) was evident at higher daily doses (90-125 mg/m^2) and therefore the BED for the daily x 5 schedule is established at 60 mg/m^2. The 25% average hypomethylation of LINE-1 compares favorably with that observed historically after Dacogen IV at the dose of 20 mg/m^2 daily x 5. The extent of LINE-1 hypomethylation after weekly x 3 SGI-110 was inferior as the maximum average hypomethylation plateaued at ~8% from baseline.

Starting at 36 mg/m^2 daily and 60 mg/m^2 weekly (44 AML, and 7 MDS patients), clinical responses were observed: 2 CRs, 1 CRp, and 1 CRi in heavily pretreated AML patients; 1 mCR and 1 HI in MDS patients previously treated with azacitidine. All responses were in patients who achieved >10% LINE-1 hypomethylation. The most common adverse events (AEs), regardless of relationship to SGI-110, were diarrhea (21%), febrile neutropenia (17%), fatigue/injection site pain/nausea at 15% each. The most common drug-related AEs were injection site pain (15%), fatigue (8%), nausea (6%), and thrombocytopenia (5%). The MTD was not reached with the weekly regimen up to 125 mg/m^2 weekly x 3. With the daily regimen, 125 mg/m^2 daily x 5 resulted in 2 dose-limiting toxicities (DLTs) of febrile neutropenia in 3 MDS patients (1 associated with bacteremia, and the other with sepsis and thrombocytopenia Grade 4) while none of the 9 patients with AML had DLT at that dose.

1.7 Potential Risks and Benefits to Human Subjects

1.7.1 Risks Based on Nonclinical Safety of SGI-110

This will be the first study of SGI-110 in humans. SGI-110 toxicity findings in rat and rabbit studies are similar to the nonclinical study findings of decitabine. Myelosuppression, decreases in thymus weight, and testicular atrophy, the main study findings of the SGI-110 studies, were also observed as the main study findings in repeat-dose toxicity studies with decitabine in mice,

rats, rabbits, and dogs. As with decitabine, myelosuppression and thymus effects after SGI-110 administration were reversible during recovery periods. Myelosuppression, particularly neutropenia, has been reported as a dose-limiting toxicity for decitabine in human clinical studies while there were no clinical evidence of testicular adverse reactions [1].

1.7.2 Risks Based on Decitabine Human Safety

The most commonly occurring adverse reactions experienced in clinical trials with decitabine are neutropenia, thrombocytopenia, anemia, fatigue, pyrexia, nausea, cough, petechiae, constipation, diarrhea, and hyperglycemia [1]. The adverse reaction profile of decitabine administered at a dose of 15 mg/m^2 by continuous IV infusion over 3 hours repeated every 8 hours for 3 days regimen is similar to the 20 mg/m^2 by continuous IV infusion over 1 hour repeated daily for 5 days every 4 weeks regimen.

For additional information regarding the toxicity profile for decitabine, please refer to the Dacogen® (decitabine for injection) prescribing information, March 2010 [1].

As no reproductive studies have been done with SGI-110, it must be considered Pregnancy Category D. Therefore, pregnant women must not take SGI-110 and female subjects must immediately stop taking the study drug if they become pregnant during treatment. Likewise, murine reproductive studies with decitabine and azacitidine suggest a negative impact on male fertility and embryonic viability. Therefore, male subjects should not father a child while receiving study drug treatment and for 2 months after the last dose of study drug.

In rare cases, anaphylactic reactions have been reported with continuous infusion IV administration.

1.7.3 Risks of SGI-110 Based on Early Clinical Data

For the most up to date clinical safety information, please refer to the most recent Investigators' Brochure.

The most common risks of SGI-110 are similar to decitabine. These include myelosuppression (neutropenia, febrile neutropenia, thrombocytopenia, and anemia) and its consequences such as fever, infection, sepsis, bacteremia, or bleeding. While in GLP toxicity studies with SGI-110 subcutaneous injections, no adverse local site reactions were noted in the multiple-dose rat and rabbit studies, clinical data indicate injection site pain, irritation, or inflammation in approximately 15% of patients. Local pain seems to be ameliorated by the use of ice packs before or after injection, injecting SGI-110 slowly instead of a push, and carefully avoiding intradermal injections.

1.7.4 Potential Benefits of SGI-110

Astex Pharmaceuticals has synthesized more stable and potent inhibitors of DNA methylation than decitabine, and demonstrated that short oligonucleotides containing an azapyrimidine effectively inhibit DNA methylation in living cells. SGI-110 was synthesized by coupling decitabine and guanosine into a dinucleotide in an attempt to improve the biological stability and thereby increase the *in vivo* efficacy of decitabine. Unlike decitabine, SGI-110 initially is resistant to deamination by cytidine deaminases until it is converted into decitabine as a result of cleavage of the phosphodiester linkage by phosphodiesterases. As such, decitabine is the active metabolite of SGI-110. It is a new chemical entity that may possess enhanced pharmacokinetic or pharmacodynamic properties compared to decitabine.

The activity of SGI-110 was demonstrated with the same preclinical pharmacodynamic assays used to demonstrate the activity of decitabine, eg, re-expression of p15, p16, and MLH1 and induction of fetal hemoglobin, *in vivo*. *In vivo* data demonstrate interspecies differences with respect to absorption, distribution, and conversion to decitabine. In xenograft studies, SGI-110 demonstrates promising nonclinical activity in hematologic malignancy and solid tumors.

As such, SGI-110 is an agent that holds promising activity in hematological malignancies given decitabine's proven activity in MDS and AML. The dosage form of SGI-110 developed for use in this study as a subcutaneous injection has the potential for a more sustained release effect compared to an IV short infusion which, in addition of being more convenient, may prolong efficacy, lower toxicity and change the PK in a beneficial way. This study, in the Dose Escalation Segment, seeks to evaluate the biological activity, preliminary safety and efficacy of SGI-110 with two dosing schedules in MDS and AML subjects while the Dose Expansion Segment will further evaluate safety and efficacy at the MTD as defined in the Dose Escalation Segment.

2.0 RATIONALE

2.1 Rationale for the Study

Hypermethylation of CpG rich regions (CpG islands) is a physiologic mechanism of permanent gene inactivation that is usurped by leukemic cells, which use it to silence tumor suppressor genes and related proteins [25]. Decitabine is a cytidine analog that profoundly inhibits DNA methylation *in vitro*, resulting in re-expression of previously silenced genes [26].

Astex Pharmaceuticals is developing SGI-110, which is a dinucleotide of decitabine and guanosine linked with a natural phosphodiester linkage. The FDA-approved drug decitabine is the active metabolite of SGI-110. Unlike decitabine, SGI-110 is resistant to deamination by cytidine deaminases. SGI-110 is cleaved by intra and extracellular phosphodiesterases releasing decitabine and natural guanosine. This may result in gradual release of decitabine both extra and intracellularly and lead to more prolonged exposures to decitabine due to potentially higher

average concentrations and longer half life. Such improved decitabine pharmacokinetics after subcutaneous administration of SGI-110 compared to direct intravenous decitabine, if achieved, may translate into better activity or safety profile of SGI-110. *In vitro* and *in vivo* studies have shown the molecule has potent antitumorigenic activity. The toxicology studies conducted to date support human testing of the molecule in subjects with hematological malignancies (MDS and AML).

2.2 Rationale for Current SGI-110 Starting Dose and Schedules

The safe starting dose of SGI-110 Regimen 1 and Regimen 2A is recommended based on the results from repeat dose toxicology studies in the most sensitive species (rabbits), results from a non-GLP non-human primate study in monkeys, other PK and safety data known for decitabine and in accordance with draft ICH Guideline S9 [27]. The recommended SGI-110 starting dose level in this study in cancer patients is 3 mg/m^2/day for the daily x 5 (Regimen 1) and 6 mg/m^2 (Regimen 2A) for the weekly x 3 of a 28-day course, respectively.

The 5-day dosing schedule was evaluated in two toxicology species, the STD_{10} was > 20 mg/kg/d in rats (120 mg/m^2/d) and the HNSTD was 1.5 mg/kg/d in rabbits (18 mg/m^2/d). Based on these studies, the recommended starting human dose for the 5-daily regimen is one sixth (3 mg/m^2) of the HNSTD in the most sensitive species (rabbit).

To support the proposal of weekly x 3 administration to cancer patients (Regimen 2A), GLP studies were also conducted with once and twice-weekly administration for three weeks in 2 species. Again, the most sensitive species was the rabbit. For the twice-weekly x 3 regimen, the STD_{10} was 30 mg/kg (180 mg/m^2) in rats, and the HNSTD was < 5 mg/kg (60 mg/m^2) in rabbits. For the once-weekly x 3 regimen, the HNSTD was 1.5 mg/kg (18 mg/m^2). However, the next higher dose level of 3 mg/kg in this study (36 mg/m^2) in the rabbits was also relatively well tolerated with the exception of one death as a result of sepsis secondary to myelosuppression. In an earlier non-GLP study in rabbits using the weekly x 3 regimen at doses 1.5, 3, 6, and 10 mg/kg, there were no mortalities at the 3 mg/kg dose level. In addition, a non-GLP study in non-human primates (4 Cynomolgus monkeys) using the higher dose level of 3 mg/kg given weekly x 3 (36 mg/m^2) was also well tolerated with only mild myelosuppression and no deaths. The decitabine exposures in Cynomolgus monkeys were much lower compared to rabbits. This is presumably due to species differences in rates of phosphodiesterase-mediated conversion of SGI-110 into decitabine. Results from an *in vitro* plasma stability study show that SGI-110 is more stable in human compared to rabbit plasma (fraction remaining after 60-min incubation of 0.5 versus 0.06 for human and rabbit, respectively). The higher plasma levels of decitabine in rabbits compared to monkeys probably explains the higher sensitivity in rabbits. In this human study, for the weekly x 3 Regimen 2A, we recommend a starting dose of 6 mg/m^2 weekly x 3 (one sixth of the 3 mg/kg or 36 mg/m^2 weekly x 3 for rabbits and Cynomolgus monkeys) based on the following observations:

- Monkeys tolerated well the 3 mg/kg weekly x 3 regimen (36 mg/m^2) and showed lower levels of decitabine than both rats and rabbits.

- There are known interspecies differences in SGI-110 and decitabine PK and that decitabine levels in humans after SGI-110 administration are more likely to resemble those of monkeys.

- In rabbits, the 3 mg/kg (36 mg/m^2) weekly x 3, while one dose level higher than the HNSTD, was well tolerated with the exception of one death that was due to sepsis secondary to myelosuppression. In an earlier non-GLP study in rabbits using the weekly x 3 regimen at doses 1.5, 3, 6, and 10 mg/kg, there were no mortalities at the 3 mg/kg dose level.

- The resulting total dose per course of the 2 regimens starting doses are comparable (15 mg/m^2 total dose for Regimen 1, and 18 mg/m^2 total dose for Regimen 2A).

- The starting doses in both regimens are much lower than the FDA-approved safe decitabine total course dose of the 5-daily regimen (100 mg/m^2 total dose). This is even more conservative considering that the molar equivalent dose to 1 mg of decitabine is 2.5 mg of SGI-110 based on molecular weight and supported by safety and efficacy data from the non-clinical pharmacology studies:

    - Starting total dose/course in Regimen 1 (15 mg/m^2) is molar equivalent to decitabine total dose of 6 mg/m^2.

    - Starting total dose/course in Regimen 2A (18 mg/m^2) is molar equivalent to decitabine total dose of 7 mg/m^2.

For Regimen 2B, the proposed starting dose of 60 mg/m^2 is the same total weekly dose that was safely achieved with the once weekly dose regimen.

Based on safety and hypomethylation results from the Dose Escalation Segment, the SRC recommended to stop the once weekly dosing schedule because of less optimal hypomethylation. The SRC also agreed to open the dose expansion in which subjects are randomized between 60 mg/m^2 and 90 mg/m^2 dailyx5. The dose of 60 mg/m^2 was chosen because it was the lowest dose that achieved maximal LINE-1 hypomethylation or BED, while the 90 mg/m^2 was chosen because it was the highest dose tolerated by both MDS and AML subjects.

A recent Phase 2 study of 53 poor-risk patients over age 60 with previously untreated AML has shown that decitabine treatment at 20 mg/m^2 IV for 1 hour on Days 1-10 had a complete remission rate of 47% (n=25) after a median of 3 cycles [28]. An additional 9 patients had no morphologic evidence of disease with incomplete count recovery, for an overall response rate of 64% (n=34) [28]. Infection and/or febrile neutropenia were common before neutrophil response and non-hematologic toxicities were infrequent. Following achievement of CR, however, infectious complications were rare.

It is hypothesized that a 10-day treatment schedule of 28-day courses of single-agent SGI-110 may improve response in subjects with relapsed/refractory AML who have no other approved treatment options. Since SGI-110 given at 125 mg/m^2 dailyx5 was tolerated by AML subjects in the Dose Escalation Segment, it was agreed by the SRC to study the 10-day dosing schedule of SGI-110 in relapsed/refractory AML subjects using the dose of 60 mg/m^2 dailyx10. This amounts to a total dose per course of 600 mg/m^2 which is similar to the total highest dose tested in the Dose Escalation Segment (125 mg/m^2 dailyx5 amounts to a total dose per course of 625 mg/m^2). Results from the 10-day regimen showed that the Overall Complete Remission rate was 30%, about double the Overall Complete Remission Rate observed with the 5-day regimen (16%) with a similar safety profile, including low 30- and 60-day mortality rates. Amendment 5 initiated the 10-day regimen in treatment-naïve elderly subjects with AML because its efficacy and safety were shown to be favorable in relapsed/refractory subjects with AML.

A course is defined as a 28-day period, with SGI-110 administered daily x 5 (Regimen 1/Dose Expansion), weekly x 3 (Regimen 2A) or twice-weekly x 3 (Regimen 2B). The treatment schedule of 60 mg/m^2 dailyx10 will also be evaluated in both relapsed/refractory and treatment-naïve AML subjects. In this treatment schedule, a course is defined as a 10-day treatment (Monday-Friday) for 2 weeks every 28 days. However, treatment delays are allowed as per Section 7.3. The first 28-day course is the period when the BED or the MTD is determined. Subjects can continue 28-day courses, but de-escalations and treatment delays will be permitted based on toxicity. Intrasubject escalations will not be allowed; however, once an MTD or BED dose level is determined, a subject may be allowed to receive their subsequent cycles at that dose level at the Investigator's discretion.

3.0 STUDY OBJECTIVES

3.1 Primary Objective

Dose Escalation Segment: Determine the overall safety profile, including dose limiting toxicities (DLTs) and determine the recommended Dose Expansion Segment regimen(s) by identifying the optimal biologically effective dose (BED) for each regimen, based on maximum global DNA hypomethylation and gene expression, OR based on the maximum tolerated dose (MTD) whichever occurs first during dose escalation.

Dose Expansion Segment: Evaluate the activity of SGI-110 as measured by overall remission rate.

3.2 Secondary Objectives

- Determine the pharmacokinetic (PK) profile of SGI-110 and decitabine.
- Remission duration, hematological improvement and transfusion independence rates.

- Determine epigenetic modulation in peripheral blood and bone marrow samples and whether any putative biomarkers (eg, cytogenetic or molecular) for SGI-110 response exists.

4.0 INVESTIGATIONAL PLAN

4.1 Overall Study Design

This study has two parts, a Dose Escalation Segment and a Dose Expansion Segment.

Subjects with intermediate or high-risk MDS or relapsed or refractory AML will be enrolled during the Dose Escalation Segment. Once a BED with acceptable safety profile or the MTD is established in the Dose Escalation Segment, the study will proceed to the Dose Expansion Segment which will allow enrollment of 1) hypomethylating agent (HMA) treatment naïve MDS (including CMML), 2) relapsed/refractory intermediate-2 or high-risk MDS (including CMML), 3) relapsed/refractory AML, and 4) treatment-naïve elderly AML subjects who fulfill the specific entry criteria shown in Section 5.0.

This study will be a multicenter, randomized, dose escalation study based on a 3 + 3 design (Figure 6) within each regimen. Each dose cohort will have at least 3-6 subjects. Eligible subjects will receive 1 of 3 dosing regimens of SGI-110 with the following starting doses:

Regimen 1: 3 mg/m^2/day subcutaneously on Days 1–5 of a 28-day course

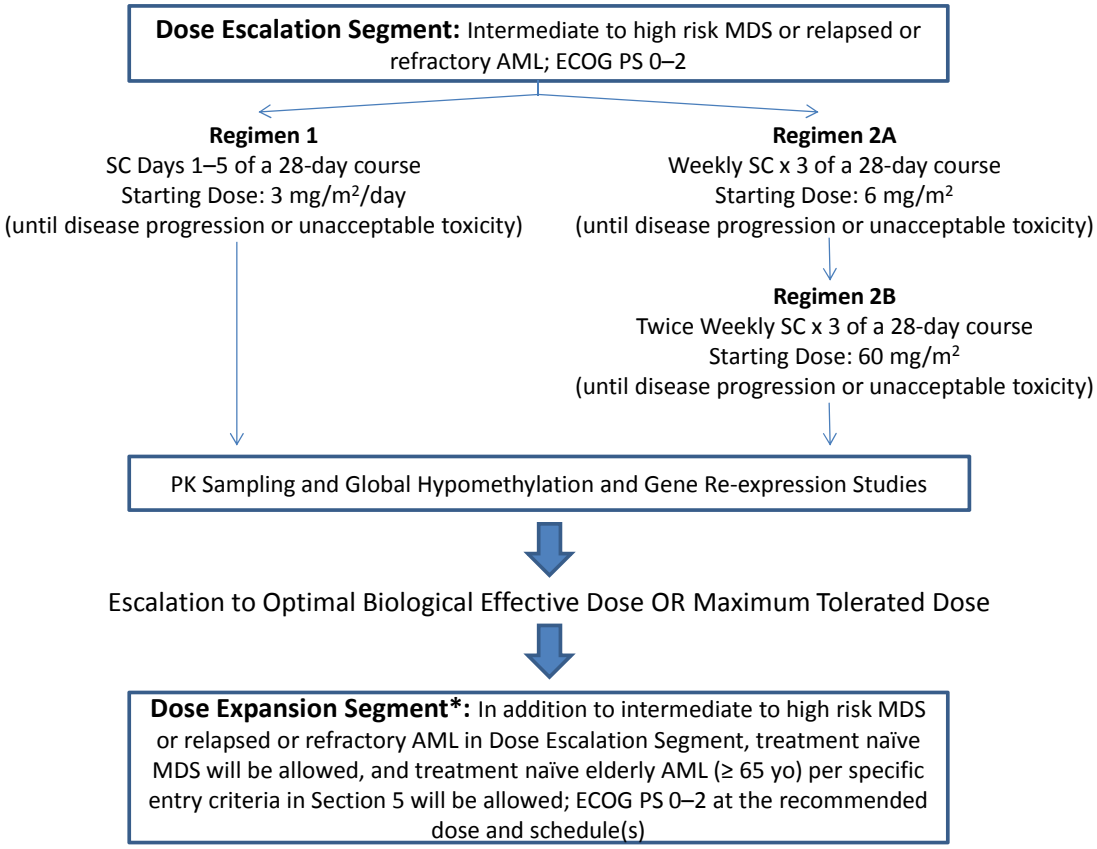
Regimen 2A: 6 mg/m^2 subcutaneously Weekly x 3 on Days 1, 8, 15 of a 28-day course

Regimen 2B: 60 mg/m^2 subcutaneously twice weekly (Days 1, 4, 8, 11, 15, 18) of a 28-day course.

In the event that one of these starting doses is not tolerated, the next lower doses would be 1.5 mg/m^2/day in Regimen 1 and 3 mg/m^2 in Regimen 2A or to be determined by the SRC in Regimen 2B.

The SRC recommended to open the Dose Expansion Segment in which MDS, treatment naïve elderly AML, and relapsed/refractory AML subjects will be randomized to receive 60 or 90 mg/m^2 dailyx5 based on preliminary results from the Dose Escalation Segment. The dose of 60 mg/m^2 dailyx5 was the BED, and the dose of 90 mg/m^2 dailyx5 was the MTD for both MDS and AML subjects. In Amendment 3, it is recommended to treat relapsed/refractory AML subjects with open-label, single-arm using 60 mg/m^2 dailyx10 which amounts to the same total dose per cycle tested in the Dose Escalation Segment using the 5-daily regimen (125 mg/m^2 dailyx5). In Amendment 5, it is recommended that treatment-naïve AML subjects receive open-label, 60 mg/m^2 SGI-110 dailyx10 in a single arm.

Figure 6: Study Schema



*The SRC recommended to randomize SGI-110 treatment to 60 or 90 mg/m^2 dailyx5 in subjects with MDS, treatment naïve elderly AML, and relapsed/refractory AML in the Dose Expansion Segment. In addition, Amendment 3 allowed a dailyx10 SGI-110 dosing schedule only in subjects with relapsed/refractory AML, and Amendment 5 allowed the dailyx10 SGI-110 dosing schedule in treatment-naïve subjects with AML, in the Dose Expansion Segment.

Pharmacokinetics will be assessed in each regimen primarily during the Dose Escalation Segment, and in 10 relapsed/refractory AML subjects, 10 MDS subjects, and up to 20 treatment-naïve AML subjects treated in the Dose Expansion Segment. If a BED or MTD is reached in one regimen before the others, all subsequent subjects will be enrolled to the remaining regimen(s) until a BED or MTD is determined for each regimen. Randomization will resume for the Dose Expansion Segment of the protocol if the decision is made to expand dosing for more than one dose or dose regimen. The Dose Expansion Segment will commence upon identification of the BED or MTD for at least one regimen.

For the protection of study subjects in the Dose Escalation Segment, the SRC including the Principal Investigators at each study center, Astex Pharmaceutical's medical monitor, and study

director will monitor, review and evaluate at least the 28-day safety data from a minimum of three subjects at each dose cohort before proceeding with the higher dose cohort.

Subsequent treatment courses could be administered as long as, in the judgment of the Investigator, the subject is still receiving benefit with acceptable toxicity. Subsequent courses may also be delayed or dose reduced based on the incidence of dose-limiting toxicities and recovery of hematological and other toxicity from previous courses.

A course is defined as a 28-day period, with SGI-110 administered daily x 5 (Regimen 1/Dose Expansion) weekly x 3 (Regimen 2A) or twice-weekly x 3 (Regimen 2B). Relapsed/refractory and treatment-naïve AML subjects will also be treated with a 10-day regimen. In this treatment schedule, a course is defined as a 10-day treatment (Monday-Friday) for 2 weeks every 28 days. However, treatment delays are allowed as per Section 7.3. The first 28-day course is the period when the BED or the MTD is determined. Subjects can continue 28-day courses, and de-escalations and treatment delays will be permitted based on toxicity. Intrasubject escalations will not be allowed; however, once an MTD or BED dose level is determined, a subject may be allowed to receive their subsequent cycles at that dose level at the Investigator's discretion.

4.2 Discussion of Study Design

MTD will be defined based on the incidence of DLTs at each dose level.

4.2.1 Definition of Dose Limiting Toxicities

The DLT is defined using the Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0) (Appendix 2). Toxicities will be considered related to SGI-110 if it cannot be reasonably explained by underlying disease, intercurrent illness or concomitant medications.

- Any study drug related Grade 3 or Grade 4 non-hematologic toxicity except Grade 3 or 4 nausea or vomiting that is controllable by anti-emetics or Grade 3 or 4 diarrhea controllable by optimal therapy such as loperamide. Grade 3 laboratory investigations other than serum creatinine, bilirubin, AST or ALT will not be considered a DLT unless they are associated with clinical manifestations.

- Study-drug related Grade 4 thrombocytopenia that was not present at study entry, that does not resolve within 7 days, and that is not related to underlying disease.

- Febrile neutropenia or Grade 4 neutropenia that was not present at study entry, that does not resolve within 7 days, and that is not related to underlying disease.

- Prolonged myelosuppression or pancytopenia with a hypocellular bone marrow and no marrow blasts lasting for 6 weeks or more that is not related to disease progression.

- Any toxicity that results in treatment delays of > 4 weeks.

All subjects who are not evaluable for toxicity in Course 1 will be replaced.

4.2.2 Safety Review Committee

A SRC will confer as the last of at least 3 subjects in a cohort completes Course 1, Day 28 in each regimen. If warranted, the committee may meet more frequently should there be any emergent safety issues. This committee will be comprised of the principal investigators (or nominated deputies), medical monitor, study director, and other study team members, as appropriate. The committee will review available safety and available PK data and recommend whether to continue the study dosing based on the protocol SGI-110 dose escalation and de-escalation guidelines (Section 4.2.3). There will be no dose escalation until the SRC meets and concurs. The SRC will make decisions regarding continuing dose escalation, or de-escalation, and expansion of cohort size to 6 or up to 12 subjects to better assess the MTD or BED during the Dose Escalation Segment of the study. The SRC will decide on the exact next dose level based on the escalation scheme provided in Section 4.2.3. The SRC may also decide to investigate other dose levels or dosing schedules if there is a consensus that it is safe to do so based on available safety data from the studied dose levels or dosing schedules at the time. Finally, the SRC will make the final determination that sufficient data are available to determine MTD, BED or other highest tolerated doses for each regimen and whether one or more regimens will move forward to the Dose Expansion Segment. If there is insufficient data at the end of the Dose Escalation Segment to declare a single recommended dose for one of the regimens to proceed to the Dose Expansion Segment, the SRC may decide to include in the randomization of the Dose Expansion Segment 2 different doses of that regimen.

A formal record of each discussion will be kept and distributed to all study sites and participants in the discussion.

As with any experimental agent, subjects may experience reactions or complications that are unknown, and therefore unpredictable. In the case of any unknown or unexpected reaction or complication, the SRC may convene to discuss and decide on the appropriate actions.

4.2.3 SGI-110 Dose Escalation

The active metabolite of SGI-110 is decitabine, an FDA-approved drug for the treatment of MDS. The reported C_{max} and $AUC_{0-\infty}$ for decitabine 20 mg/m^2 IV infusion over 1 hour daily for 5 days (n=11) was 147 ng/mL and 115 ng*h/mL, respectively [1]. Therefore, Astex Pharmaceuticals proposes the following dose escalation scheme for each regimen:

- 100% increments until 50% of the reported (for the approved dose) mean C_{max} of decitabine (74 ng/mL) OR 50% of the mean $AUC_{0-\infty}$ (58 ng*h/mL) is reached provided that no DLTs are observed.

- In the absence of DLTs, once a decitabine mean C_{max} of 74 ng/mL OR mean $AUC_{0-\infty}$ of 58 ng*h/mL is reached, then the escalation will follow the sequence of 67%, 50%, 40%, and 33% increments thereafter. For Regimen 2B, escalation, if approved by SRC, will proceed only at 33% increments and only if it shows better hypomethylation levels than the once weekly regimen (Regimen 2A) and are similar to the daily regimen as determined by SRC review.

- If no DLTs occur in any subject, enrollment of subjects at the next dose level will occur.

- In the presence of one DLT in any subject, the cohort will have at least 6 subjects and then escalation may continue only as 33% increments or lower as decided by the SRC.

- In the presence of two or more DLTs in two or more subjects in one cohort, dose escalation will be stopped.

The MTD will be defined as the largest dose for which fewer than 33% of subjects experience a DLT during Course 1 of SGI-110 administration during the study. The BED will be defined as the smallest dose that achieves a maximum hypomethylation or gene expression in at least three successive dose levels.

Escalation to subsequent levels will not occur until at least 3 subjects in the previous dose level complete the first 28-day course of treatment and safety data and pharmacokinetic (C_{max} and AUC) parameters have been assessed by the SRC. At the recommended Dose Expansion Segment dose(s) and schedule(s), a minimum of 30 subjects will be enrolled in each of the following 6 subgroups: 1) HMA treatment-naïve MDS (including CMML); 2) relapsed/refractory intermediate-2 or high-risk MDS (including CMML); 3) refractory/relapsed AML treated with the 5-day regimen; 4) refractory/relapsed AML treated with the 10-day regimen; 5) treatment-naïve elderly AML treated with the 5-day regimen; and 6) treatment-naïve elderly AML treated with the 10-day regimen. The SRC for a particular subgroup, where the most number of responses are observed, may increase the number of subjects up to 50 subjects per subgroup to have a better assessment of efficacy in that subgroup. One or more dose or dose regimen may go forward to the Dose Expansion Segment of this study based on the results of the Dose Escalation Segment and review of all relevant data by the SRC. Subjects can continue in subsequent courses as long as in the judgment of the Investigator, they are receiving benefit with acceptable toxicity. During the Dose Escalation Segment, the SRC may decide to enroll more patients at a given dose level or dosing schedule to better assess safety before escalation.

4.2.4 Global DNA Hypomethylation and Gene-Specific Re-Expression

Collection of blood samples pre-dose Day 1, and pre-dose each day at Days 8, 15, and 22 during Course 1 and pre-dose at Day 1 of Course 2 will be an integral part of the study. Blood RNA and

DNA will then be analyzed for the following hypomethylation and gene-specific re-expression markers:

- Gene specific expression (p15INK4b)
- Global DNA hypomethylation in LINE-1 sequence
- Other gene expression markers: miRNA-124a, ataxia telangiectasia mutated (ATM)
- Additional biomarkers as they become known

4.3 Study Endpoints

4.3.1 Primary Endpoints

Dose Escalation Segment: Optimal BED as assessed by global DNA hypomethylation and gene-specific re-expression, or the MTD as assessed by Common Terminology Criteria for Adverse Events (CTCAE version 4.0) for each regimen.

Dose Expansion Segment: Overall remission rate as measured by the IWG 2006 MDS Response Criteria [2] and 2003 AML Response Criteria [3] (Section 9.6).

4.3.2 Secondary Endpoints

- Incidence and severity grades of DLTs and other adverse events, and abnormal laboratory values
- C_{max}, C_{min}, AUC and other PK parameters of SGI-110 and decitabine
- Rates of hematologic improvement and duration of remission
- Time to AML or death (only for MDS subjects)
- Overall survival
- Incidence of blood and platelet transfusions

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Number of Subjects

The number of subjects enrolled during the Dose Escalation Segment of the study will depend on the number of dose levels necessary to achieve either BED or MTD based on the study's escalation scheme. It is estimated that the Dose Expansion Segment will enroll up to 30 subjects per disease subgroup (relapsed/refractory AML; treatment-naïve elderly AML as per eligibility criteria described in Section 5.0; HMA treatment-naïve MDS including CMML; and

relapsed/refractory intermediate-2 or high-risk MDS including CMML) for each dose and dose regimen approved to proceed to the Dose Expansion Segment by the SRC. The SRC may also decide in expanding one or more disease subgroup to 50 subjects if justified by promising efficacy and safety data. The SRC recommended to expand the sample size of relapsed/refractory AML subjects to include up to 50 subjects randomized to 60 mg/m^2 and 90 mg/m^2 dailyx5, with up to 50 subjects to be treated with a single arm using 60 mg/m^2 dailyx10. Based on favorable results from the relapsed/refractory AML cohort treated with the 10-day regimen, Amendment 5 expanded the sample size of treatment-naïve subjects with AML to include at least 30 subjects, and up to 50 subjects, to be treated with a single arm using 60 mg/m^2 dailyx10 similar to the other arms in the study.

Investigators must keep a record of subjects who signed a consent form but failed screening procedures or decided not to enroll after signing the consent.

Activities to confirm whether a subject is eligible to participate in this study can only be conducted after the subject has signed the institutional review board (IRB)–approved informed consent form (ICF) confirming their willingness to participate in this trial. Screening evaluations will be performed within 14 days prior to the subject's first dose of SGI-110.

5.2 Inclusion Criteria

To be eligible for the study, subjects must fulfill all of the following criteria. The investigator or a sub-investigator must ascertain a subject's eligibility strictly according to these criteria before they receive their first dose of SGI-110.

1. Subjects who are men or women, 18 years of age or older, with a confirmed diagnosis of IPSS intermediate-1, intermediate-2 or high-risk MDS including Chronic Myelomonocytic Leukemia (CMML), or AML.

    a) In the Dose Escalation Segment, subjects who are refractory, relapsed, or unresponsive to standard treatment will be the only ones allowed.

    b) In the Dose Expansion Segment, HMA treatment naïve MDS subjects (including CMML), and intermediate-2 or high-risk MDS subjects (including CMML) relapsed or refractory to prior HMA treatment are allowed, and treatment naïve AML subjects who are at least 65 years of age will be allowed if they also have at least one of the following criteria:

        1) AML secondary to MDS, chemotherapy, or radiation therapy,

        2) poor cytogenetics defined as monosomies or partial deletions of chromosome 5 or 7 (del(5q), del(7q), -5, -7), abnormalities involving the long arm of chromosome 3 (q21;q26), t(6;9) (p23;q34), t(9;22) (q34;q11.2), or abnormalities including the

long arm of chromosome 11 (11q23), or subjects with 3 or more unrelated cytogenetic abnormalities of any kind,

3) 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 [FEV1] < 50% of expected) which is unrelated to the leukemia.

4) poor performance status, Eastern Cooperative Oncology Group (ECOG), of 2

5) age ≥75 years

2. Subjects with ECOG performance status of 0 to 2.

3. Subjects with adequate organ function, defined as:

   a) Hepatic: Total bilirubin ≤ 2 X upper limit of normal (ULN); aspartate transaminase (AST/SGOT) and alanine transaminase (ALT/SGPT) ≤ 2.5 X ULN.

   b) Renal: serum creatinine ≤ 1.5 X ULN.

4. Women of child-bearing potential must not be pregnant or breastfeeding and must have a negative pregnancy test at screening. Woman of child-bearing potential and all men must be practicing two medically accepted methods of birth control. Women of non-childbearing potential are those having hysterectomy; bilateral oophorectomy; or menopause defined as no menses for at least 1 year AND either age ≥ 65 years or follicle-stimulating hormone (FSH) levels in the menopausal range.

5. For subjects with prior allogeneic stem cell transplant, no evidence of active graft-versus host disease (GVHD) and must be ≥ 2 weeks off immunosuppressive therapy.

6. Subjects with no major surgery within 4 weeks of first dose of SGI-110.

7. Subjects with no chemotherapy within 2 weeks of first dose of SGI-110 (minimum of 6 weeks for nitrosoureas and 8 weeks for bone marrow transplantation) with the exception of hydroxyurea which will be allowed during Course 1 of treatment.

8. Subjects who sign an approved informed consent form for the study.

9. Subjects who are willing to comply with the protocol.

5.3 Exclusion Criteria

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

1. In the Dose Expansion Segment, which includes the 10-day regimen, subjects who have received 2 complete full dose cycles or more of a HMA decitabine or azacitidine (except for intermediate-2 or high-risk MDS subjects (including CMML) relapsed or refractory to prior HMA treatment).

2. Subjects with acute promyelocytic leukemia (M3 classification).

3. Subjects with prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for at least 3 years.

4. Subjects with a life-threatening illness other than MDS or AML, uncontrolled medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, or put the study outcomes at risk.

5. Subjects with uncontrolled or symptomatic arrhythmias, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification.

6. Subjects with symptomatic central nervous system (CNS) metastases or lesions for which treatment is required.

7. Subjects who have received prior radiation therapy for extramedullary disease within 2 weeks of randomization.

8. Subjects with Grade $\geq$ 2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation.

9. Subjects with known history of human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV).

10. Subjects who have been treated with any investigational drug within 2 weeks of randomization.

11. Subjects who are being treated with systemic corticosteroids as treatment for their MDS or AML. Corticosteroids treatment for other conditions is allowed.

12. Subjects with uncontrolled active systemic infections.

13. Subjects who have hypersensitivity to decitabine, SGI-110, or SGI-110 excipients.

14. With the exception of treatment-naïve elderly AML subjects, where certain co-morbidities are allowed per Inclusion Criterion #1b, subjects with uncontrolled CHF, CAD, COPD, or LVEF of $\leq$ 50% are excluded.

5.4 Withdrawal of Subjects from Study Treatment

Subjects can voluntarily withdraw at any time during the study. Subjects may withdraw from study treatment but still continue study follow-up procedures. Investigators are encouraged to keep a subject experiencing clinical benefit in the study unless significant toxicity puts the subject at risk or significant noncompliance or intercurrent illness that puts the study outcomes at risk. Specifically, if the subject meets any 1 of the following criteria then he or she should be withdrawn from the treatment:

- Disease progression, unless in the Investigator's judgment, the subject may still benefit from treatment.
- DLT that does not improve to baseline or to ≤ Grade 1 level for 4 weeks or more or subject experiencing a second DLT after dose reduction (see Section 4.2.1 for definition of DLT)
- Any toxicity that results in delay of dosing for more than 4 weeks, except if it's in the subject's best interest to continue SGI-110 administration as judged by the Investigator based on clinical benefit
- Subject becomes pregnant
- It is in the subject's best interest according to the Investigator's clinical judgment

Astex Pharmaceuticals may request that a subject is withdrawn for safety reasons or for non-compliance. If a subject prematurely withdraws from study treatment, the reason(s) for withdrawal must be recorded on the relevant page of the subject's case report form (CRF).

It is important to obtain follow-up information on any subject withdrawn prematurely from study treatment. Every effort must be made to undertake protocol specified follow-up procedures. For subjects willing to continue study follow-up procedures, the Investigator should review the follow-up procedures with the subject, including the number of visits, the specific procedures to be done, and the total length of the follow-up period. 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 for the entire study period.

If a subject refuses to undergo the study follow-up procedures, the reason for refusal should be fully documented. Subjects who refuse to continue study procedures should, if at all possible, undergo all end of study assessments.

Subjects taken off study before completion of Course 1 for reasons other than toxicity will be replaced.

6.0 RANDOMIZATION

6.1 Subject Randomization and Treatment Assignment

Subjects will be randomized to one of each available regimen in the Dose Escalation Segment. Regimen 2B in the Dose Escalation Segment was added later so it was not part of the initial randomization. If MTD or BED is reached in one regimen before the others, then all new enrolled subjects will be assigned to the remaining regimen(s) until MTD or BED is also reached in each regimen. Subjects who are eligible for the Dose Expansion Segment of study will be randomly allocated to one of the dose or dose regimens approved to proceed to dose expansion by the SRC. Randomization will be performed by Astex Pharmaceuticals randomization procedure as close as possible to treatment and should not exceed 1 week of the planned dose if more than one regimen goes forward. The assignment will not be blinded. It is recommended that study treatment be started as soon as possible after subjects are assigned to a treatment.

Subject randomization will only be allowed for authorized investigators who have been qualified by Astex Pharmaceuticals. After the investigator or sub-investigator confirms that a subject is eligible and willing to participate in the study, site personnel will forward the appropriate documentation to the attention of the SGI-110 Project Manager or designee as delineated in the SGI-110-01 Study Manual.

The Subject ID Number, Regimen, and assigned dose level will be sent to the study center via email or other traceable communication route.

Stratification will occur by disease type (MDS vs. AML) in the Dose Escalation Segment, and by disease type (MDS vs. AML) and prior treatment (AML: treatment-naïve vs. previously treated; MDS: HMA treatment-naïve vs. multiple courses of HMA treatments) in the Dose Expansion Segment of this study. For MDS subjects, the "HMA treatment-naïve" means having received fewer than 2 full dose cycles of an HMA treatment, whereas multiple courses of HMA treatments means having received at least 2 complete full dose cycles of an HMA. One or more dose or dose regimen may go forward to the Dose Expansion Segment of this study based on the results of the Dose Escalation Segment and review of all relevant data by the SRC. If only one regimen is allowed to move forward by the SRC, then all subjects will be enrolled in that regimen with no randomization.

7.0 STUDY TREATMENTS

7.1 Investigational Drug

7.1.1 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

7.1.2 Packaging and Labeling

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

SGI-110 for Injection, 100 mg is a 5 mL glass vial containing lyophilized SGI-110 drug powder for reconstitution and subcutaneous injection using the custom diluent supplied in a separate vial. Each vial is stoppered with fluropolymer coated butyl rubber closure and sealed with a blue flip-off cap. *SGI-110 for Injection, 100 mg* vial is individually packaged in a heat-sealed aluminum foil pouch with a single desiccant bag to protect from moisture.

SGI-110 Diluent for Reconstitution, 3 mL is a 5 mL glass vial with 3 mL of custom diluent. Each vial is stoppered with fluropolymer coated butyl rubber closure and sealed with a white flip-off cap.

7.1.3 Drug Handling and Storage

SGI-110 for Injection, 100 mg vial is stored at refrigerated condition of 2–8ºC in the original packaging until use. *SGI-110 Diluent for Reconstitution, 3 mL* can be stored at 2–30ºC in upright position until use. Both vials are preservative free and for single use only.

OSHA Guidelines for handling cytotoxic drugs outlined in the American Journal of Hospital Pharmacy must be followed [29]. As with other potentially toxic anti-cancer agents, care should be exercised in the handling and preparation of SGI-110. The use of gloves and protective garments is recommended. Preparation should occur in a vertical laminar flow biological hood using proper aseptic technique. If SGI-110 contacts the skin, it should be immediately be treated with borax buffer solution pH 10 followed by washing immediately and thoroughly with soap and water. If SGI-110 contacts the mucous membranes, flush thoroughly with water.

Drug spilling can be inactivated by 2 N sodium hydroxide solution.

7.1.4 Drug Reconstitution and Stability

Reconstituted drug product is intended for subcutaneous administration at a maximum concentration of 100 mg/mL. The required volume from the diluent vial is drawn into a syringe for reconstitution and emptied into the vial containing SGI-110 for injection. The vial with reconstituted SGI-110 must be vortexed for at least 30 min using a laboratory vortex machine before use. Reconstituted SGI-110 is stable in 2–8ºC for up to 8 days provided that the vial is stored immediately in refrigerated conditions upon reconstitution. Further details on drug reconstitution can be found in the SGI-110 Pharmacy Manual.

7.2 Drug Regimens and Administration

The study initially investigated 2 regimens:

Regimen 1: SGI-110 given SQ daily for 5 days in a 28-day course. The recommended starting dose for that regimen is 3 mg/m^2/d for 5 days (total starting dose per course is 15 mg/m^2).

Regimen 2A: SGI-110 given SQ weekly for 3 injections (Days 1, 8, and 15) on a 28-day course. The recommended starting dose for that regimen is 6 mg/m^2 weekly for 3 weeks (total starting dose per course is 18 mg/m^2).

A third regimen (Regimen 2B) was later added: The starting dose is 60 mg/m^2 twice weekly given subcutaneously for 3 weeks on (Days 1, 4, 8, 11, 15, 18) of a 28-day course.

In the Dose Expansion Segment, subjects will be randomized between 60 mg/m^2 dailyx5 and 90 mg/m^2 dailyx5 for a minimum of 30 subjects in each of 1) HMA treatment-naïve MDS (including CMML), 2) relapsed/refractory intermediate-2 or high-risk MDS (including CMML), 3) treatment-naïve elderly AML, and 4) relapsed/refractory AML subjects as per the study eligibility criteria described in Section 5.0. Up to 50 relapsed/refractory AML subjects, and up to 50 treatment-naïve AML subjects, will be treated with single arm 60 mg/m^2 dailyx10. To avoid dosing on weekends, the dailyx10 regimen will be given over two weeks in which treatment is given 5 days each week Monday-Friday.

SGI-110 is administered by subcutaneous injection preferably in the abdominal area. The total amount (in mg) of study treatment to be administered in the Dose Escalation Segment and the Dose Expansion Segment will be determined based on the body surface area (BSA). In calculating the BSA, actual heights and weights should be used. There will be no adjustments to "ideal" body weight. Appendix 3 provides a BSA nomogram as an example to be used for BSA determination. The institutional standard for calculating BSA is acceptable.

The site(s) of injections will be captured on the dosing CRF. Additional guidelines regarding subcutaneous injection will be detailed in the SGI-110-01 Study Procedures Manual.

Investigators are prohibited from supplying SGI-110 to any subjects not properly enrolled in this study or to any physicians or scientists except those designated as sub-investigators on Food and Drug Administration (FDA) Form 1572. The investigator must ensure that subjects receive SGI-110 only from personnel who fully understand the procedures for administering the study treatment.

7.3 Criteria for Adjusting or Withholding Study Drug Dosing

In the Dose Escalation Segment, if the subject has already received treatment on Day 1, subsequent treatment days (Day 2-5 in the 5-day regimen, and Days 8, or 15 in the weekly regimen) will be withheld if the subject develops any DLT as defined in Section 4.2.1 and the skipped doses will be missed. Dosing will also be withheld on Day 1 of any subsequent treatment courses if the subject still has a DLT or other drug-related clinically significant toxicity that has not resolved to baseline or ≤ Grade 1 or have become ineligible by the protocol inclusion

criteria in Section 5.2. Dosing may restart once the subject becomes eligible again and the DLT or other drug-related toxicity has resolved to either baseline or ≤ Grade 1. If dosing is delayed by more than 4 weeks, then the subject will be withdrawn from treatment unless it is judged to be in the subject's best interest to continue by the Investigator based on clinical benefit. If the subject has a DLT and it has resolved, he or she may be redosed for subsequent courses only at the next lower dose level. If this happens at the first dose level then the subject will receive 50% of that dose.

In the Dose Expansion Segment, similar guidelines should be followed for MDS subjects. For AML subjects treated with the dailyx5 or the dailyx10 regimen, physicians should attempt to give the full intended dose for at least 2 courses for the 10-day regimen, and at least 4 courses for the 5-day regimen but the course could be extended from 28 days to up to 42 days to allow for marrow recovery in case of significant marrow hypocellularity. Additional delay or dose reduction may be applied based on investigator's judgment.

7.4 Concomitant Medications

7.4.1 Allowed Therapies and Treatments

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

7.4.1.1 Antibiotics

Antibiotics may be utilized to prevent or manage febrile neutropenia based on institutional standard practice. Febrile neutropenia is defined as temperature at least 38.5ºC when the ANC is < 1000 µL. Febrile subjects are be evaluated by physical examination, CBC with differential, and blood culture. Subjects with febrile neutropenia or suspected sepsis on the basis of the physical examination are to be hospitalized for appropriate broad spectrum antibiotic coverage, consistent with local pathogen sensitivities.

7.4.1.2 Hematopoietic Growth Factors

Hematopoietic growth factors will not be routinely used. However, its use is permitted if deemed to be medically necessary by the treating physician. Erythropoietin can be used after Course 1. Use of these agents should be guided by accepted practice or institutional guidelines.

7.4.1.3 Hydroxyurea

Hydroxyurea will be allowed for all subjects during Course 1 of treatment. Thereafter, hydroxyurea will not be allowed for any subject on study.

7.4.2 Prohibited Medications

Prohibited concomitant therapies while on study are: radiation therapy, chemotherapy, immunotherapy, hematopoietic growth factors unless for emergency use or if judged by the investigator to be clinically necessary (erythropoietin can be used after Course 1), or any experimental therapy.

7.5 Overdose Instructions

Any dose of study treatment in excess of that specified in this protocol is considered to be an overdose. Regardless of presence or absence of clinical symptoms, an overdose must be reported as an AE to Astex Pharmaceuticals Drug Safety in the same manner as any SAE (see Section 10.3). Signs and symptoms of an overdose that meet any SAE criterion also must be reported as an SAE in the appropriate time frame and documented as clinical sequelae to an overdose. Treatment of AEs associated with overdose should be supportive for the underlying symptoms. As this is the first-in-human study of SGI-110, no data are available regarding the overdosage of SGI-110. Based on the clinical experience of decitabine, an overdosage of SGI-110 may result in more profound or prolonged myelosuppression and patients should be managed accordingly.

8.0 RISKS/PRECAUTIONS

8.1.1 Drug-drug Interactions

Drug-drug interaction studies have not been conducted with SGI-110 or decitabine. *In vitro* studies in human liver microsomes suggest that decitabine is unlikely to inhibit or induce cytochrome P450 enzymes. Thus, drug-drug interactions are not anticipated for SGI-110.

8.1.2 Genotoxicity

SGI-110 may be genotoxic, which could cause fetal harm. Therefore, subjects with reproductive potential must use 2 reliable, approved methods of contraception simultaneously (1 of the 2 forms of effective contraception should be non-hormonal) during the study and for 60 days after the last dose of SGI-110. Subjects should promptly notify the investigator if they, or their partner, become pregnant during this period. If a female subject becomes pregnant during the treatment period, she must discontinue SGI-110 immediately. Pregnancy in a female subject or a male subject's partner must be reported in the same manner as any SAE (see Section 10.3 and Section 10.2.3) using Pregnancy Forms I and II and, if applicable, an SAE Form.

9.0 STUDY PROCEDURES

The complete schedule of events for Regimen 1, Regimen 2A, Regimen 2B and the recommended 10-day schedule is shown in Table 2 and detailed in the text that follows. Table 2 shows all assessments and procedures for ≥ Course 2. Additional information on the study procedures is provided in the study procedures manual. With the exception of the pharmacokinetic assessments, study procedures conducted at each visit are the same for subjects enrolled in the Dose Escalation Segment and the Dose Expansion Segment of the trial.

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

Any deviation or violation from protocol procedures should be noted and the Astex Pharmaceuticals Clinical Program Manager should be notified. It is the Investigator's responsibility to implement appropriate measures to prevent the recurrence of deviations.

Table 2: Schedule of Events

Courses (28 Days)[a]		1[a]													≥ 2[a]													Term	30FU[b]	Survival
Course Day		1	2	3	4 (±1)	5	8 (±2)	9	10	11 (±1)	12	15 (±2)	18 (±1)	22 (±2)	1	2	3	4 (±1)	5	8 (±2)	9	10	11 (±1)	12	15 (±2)	18 (±1)	22 (±2)			
Regimen 1 and Dose Expansion: SGI-110 on Days 1-5		x	x	x	x	x									x	x	x	x	x											
Regimen 2A: SGI-110 Weekly x 3		x					x					x			x					x					x					
Regimen 2B: SGI-110 Twice Weekly x 3		x			x		x			x		x	x		x			x		x			x		x	x				
Dailyx10 Regimen: SGI-110 on Days 1-5 and 8-12[a]		x	x	x	x	x	x	x	x	x	x				x	x	x	x	x	x	x	x	x	x						
Procedures	**Screening[c] (D-14 to D-1)**																														
Informed consent	x[c]																														
Medical history	x																													
Concomitant medications/adverse events	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	x	x	x	x	x	
Transfusion requirements[d]	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	x	x	x	x	x	
Investigator's confirmation of eligibility	x																														
Physical exam/symptom-directed PE[e]	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		x	x	
Vital signs[f]	x	x	x[f]	x[f]	x[f]	x[f]	x[f]	x[f]	x[f]	x[f]	x[f]	x[f]	x[f]		x	x[f]	x[f]	x[f]	x[f]	x[f]	x[f]	x[f]	x[f]	x[f]	x[f]	x[f]		x	x	
ECOG status	x	x													x													x	x	
12-lead ECG[g]	x	x													x[g]															
ECHO or MUGA[h]	x																													
Bone marrow aspirate or biopsy	x[i]																													
Height	x																													
Weight and BSA calculation (use height from screening)[j]		x													x															
Laboratory Assessments																														
Hematology[k]	x	x					x					x		x	x					x					x		x	x		
Chemistry[l]	x	x													x													x		
Urinalysis[m]	x																													
Serum or urine pregnancy test[n]	x																											x		
Pharmacokinetics[o]		x[o]	x[o]	x[o]	x[o]	x[o]	x[o]				x[o]																			
Epigenetics[p]		x[p]					x					x		x	x															
Buccal swab[p]		x[p]																												
Pharmacogenetic markers[q]		x																												
Disease Assessments																														
Response assessment[r]		Review CBC at the end of every course.																										x		
Bone marrow aspirate or biopsy[s]		To evaluate responses: CR, CRp, CRi or PR. Otherwise, at the Investigator's discretion.																										x		
Conversion to AML (MDS subjects); and survival follow up[t]		At the end of every course.																												x

a. **The visit schedule and assessments** are at the investigator's discretion after Course 6; however, all adverse event and dosing information must be collected. Dailyx10 dosing is Mon-Fri and there will be no visit windows on the treatment dosing days in this regimen.

b. **30-day Follow-up Visit:** must occur 30 (+5) days after the last dose of SGI-110. For 30-day follow-up via telephone, perform only assessment of new AEs.

c. **Screening:** must occur within 14 days of first dose of SGI-110. Informed consent can be obtained within 28 days before the start of study drug administration.

d. **Transfusion requirements:** Document all blood and platelet transfusions from 28 days before the start of the study drug administration (Course 1, Day 1) through 30 days after the last dose of study drug.

e. **Physical exam/symptom-directed physical exam:** Complete physical exam includes weight and examination of body systems per institutional standards. A complete physical exam will be performed on Screening, Day 1 of each course thereafter irrespective of the regimen, and the Termination Visit. Course 1, Day 1 complete physical exam does not need to be repeated if it was done up to 4 days before the first dose of SGI-110. A symptom-directed physical exam will be done on dosing Days 2-5 in Regimen 1, on dosing Days 8 and 15 in Regimen 2A, on dosing Days 4, 8, 11, 15 and 18 in Regimen 2B, on dosing Days 2-5 and 8-12 in the Dailyx10 regimen, and the 30-day Follow-up Visit irrespective of regimen.

f. **Vital signs:** includes resting systolic/diastolic blood pressure, resting respiration rate, resting heart rate, and body temperature. Assess after the subject has rested in the sitting position for at least 3 minutes. Vital signs are required daily on dosing Days 1-5 for Regimen 1, weekly on dosing days for Regimen 2A and on all dosing days for Regimen 2B and the 10-day schedule.

g. **12-Lead ECG:** acquired and reviewed according to the study site's standard procedure. Either the Bazett's or Fridericia's formula may be used to calculate the QTc interval but must be consistently used throughout the study. Course 1, Day 1 ECG does not need to be repeated if it was done up to 4 days before the first dose of SGI-110. After Course 4, ECG is only as needed at the investigator's discretion.

h. **ECHO or MUGA:** Either is acceptable as long as the same method is used consistently throughout the study.

i. **Screening bone marrow aspirate or biopsy:** bone marrow aspirate or biopsy differential will be performed according to local standard practice. The screening bone marrow aspirate must occur within 28 days of the first dose of study drug. A bone marrow biopsy can be done if no aspirate is available. Bone 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
- Megakaryocytes
- M:E ratio
- Myeloid and erythroid maturation
- Presence of dysplasia
- Cellularity: % cellularity; hypocellular, hypercellular, normocellular
- Other

An anonymized report of all bone marrow testing results will be submitted to Astex Pharmaceuticals. A portion of Screening bone marrow aspirates will be used for assessing epigenetics of the study drug. Peripheral, Geimsa and Iron stained slides to be provided with each bone marrow aspirate or biopsy. Information regarding the collection, labeling and shipping instructions can be found in the Study Lab Manual. Cytogenetics will be reviewed on the screening bone marrow and should include at least 20 clones. If cytogenetics are abnormal, they must be reviewed again in subsequent bone marrow aspirates or biopsies.

j. **BSA (see** Appendix 3**):** calculate on Day 1 of each course. If a subject has a notable change in weight (eg, loss or gain of ≥ 10%) within a course, then recalculate subject's dose at that time.

k. **Hematology:** must include complete blood count with manual differential and platelet counts. Course 1, Day 1 hematology evaluation does not need to be repeated if it was done up to 4 days before the first dose of SGI-110. On Course 1, all hematology evaluations must meet study entry criteria before dosing. Collection, analysis and reporting information can be found in the Study Lab Manual. Additional labs may be drawn at the Investigator's discretion for clinical interventions.

l. **Chemistry:** must include glucose, calcium, magnesium, albumin, total protein, sodium, potassium, CO2, chloride, blood urea nitrogen, creatinine, lactate dehydrogenase, alkaline phosphatase, ALT, AST, and total bilirubin. Course 1, Day 1 chemistry evaluation does not need to be repeated if it was done up to 4 days before the first dose of SGI-110. On Course 1, Day 1 all chemistry evaluations must meet study entry criteria before dosing. Collection, analysis and reporting information can be found in the Study Lab Manual. Additional labs may be drawn at the Investigator's discretion for clinical interventions.

m. **Urinalysis:** Includes microscopic examination. Urinalysis at Screening and thereafter only as needed at the investigator's discretion.

n. **Pregnancy test:** only for women of child-bearing potential.

o. **PK Sampling:** Refer to Section 9.2.1.

p. **Epigenetic testing:** includes but is not limited to LINE-1, p15INK4b, miRNA124a, and ATM. Draw blood samples for epigenetic testing pre-dose Day 1, and pre-dose each day at Days 8, 15, and 22 during Course 1 and pre-dose at Day 1 of Course 2. A buccal swab will be taken before the first dose of study drug. Information about sample collection and storage is in the Study Lab Manual.

q. **Pharmacogenetic markers:** Includes but not limited to hENT-1 and -2, dCK, and cytidine deaminase. On Course 1 Day 1 only. Information about sample collection and storage is in the Study Lab Manual.

r. **Response assessment:** Refer to Section 9.7 for the appropriate disease assessment. At the end of every course prior to the initiation of the next course and the Termination Visit.

s. **Bone marrow aspirate or biopsy:** Bone marrow aspirate must be done to verify first CR, CRp, CRi or PR immediately when peripheral counts suggest a response, and at least every other cycle as long as the subject continues to be responding. Otherwise, done at the Investigator's discretion. Bone marrow aspirate or biopsy differential will be performed according to local standard practice (see Footnote i). A portion of all on-study bone marrow aspirates will be used for biomarker identification. A bone marrow biopsy can be done if no aspirate is available. Cytogenetics will be performed on every bone marrow examination. Peripheral, Geimsa and Iron stained slides to be provided with each bone marrow aspirate or biopsy.

t. **Conversion to AML (MDS subjects); and Survival follow-up:** at the end of every course during treatment. Every 3 months after stopping study treatment.

9.1 Screening Assessments All Subjects (Regimen 1, 2A and 2B, Dose Expansion and 10-Day Schedule)

A screening visit is to be conducted within 14 days before the first study treatment dose (except for bone marrow aspirate or biopsy and informed consent which will be allowed within 28 days from treatment). The following evaluations are to be performed and samples are to be collected at the Screening visit:

- Provision of written informed consent within 28 days before the start of study drug administration. The informed consent form must be signed and dated by the subjects before collection of any samples or performance of any study evaluations.

- Complete medical history, including demographics (date of birth, sex, race), treatment history for MDS and AML, response to such treatment, and the criteria used to determine such a response and other pertinent medical conditions, medications, and supportive therapies. A disease history, including the date of initial diagnosis and list of prior treatments and responses to these treatments, also will be recorded. Concurrent medical signs and symptoms must be documented to establish baseline severities.

- Record concomitant medications.

- Record all study-procedure related AEs from the time of informed consent and then treatment-emergent AEs after the start of study drug administration (Course 1, Day 1) through 30 days after the last dose of study drug.

- Record transfusion (within 28 days from treatment).

- Investigator's confirmation of eligibility. Perform all necessary procedures and evaluations to document that the subject meets each eligibility criterion.

- Complete physical exam including weight and examination of body systems per institutional standards.

- Vital signs include resting systolic/diastolic blood pressure, resting respiration rate, resting heart rate, and body temperature. Assess after the subject has rested in the sitting position for at least 3 minutes.

- ECOG performance status.

- 12-lead ECG (rhythm, ventricular rate, PR interval, QRS duration, and QT/QTc).

- ECHO or MUGA (either is acceptable as long as the same method is used consistently throughout the study).

- Bone marrow aspirate or biopsy (include sample for methylation studies). Peripheral, Geimsa and Iron stained slides to be provided with each bone marrow aspirate or biopsy.
- Bone marrow cytogenetics (cytogenetics should include at least 20 clones).
- Height.
- Sample collection for clinical laboratory tests, including:
  - Hematology: complete blood count (CBC) with manual differential and platelet counts.
  - Chemistries: glucose, calcium, magnesium, albumin, total protein, sodium, potassium, CO2, chloride, blood urea nitrogen, creatinine, lactate dehydrogenase, alkaline phosphatase, ALT, AST, and total bilirubin.
- Urinalysis: Urinalysis must include microscopic examination.
- Serum or urine pregnancy test: for female subjects of child-bearing potential only. Results must be negative for the subject to be eligible for enrollment into the study.

9.2 Treatment Assessments

9.2.1 Pharmacokinetic Assessments

Pharmacokinetics (PK) of both SGI-110 and decitabine will be assessed for each regimen during the Dose Escalation Segment, and in 10 relapsed/refractory AML subjects, 10 MDS subjects, and up to 20 treatment-naïve AML subjects treated in the Dose Expansion Segment.

9.2.1.1 Regimen 1 (QD x 5)

- Course 1, Day 1 and Day 5: pre-dose, 15 min, 30 min, 60 min, 90 min and 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, and 24 hr post-dose (pre-Day 2 for Day 1 samples)
- Course 1, Days 2–4: pre-dose

For Dose Expansion PK, the following time points are not required: Course 1, Day 1 24-hr post-dose; Course 1, Days 2-4; and Course 1, Day 5 pre-dose time points.

9.2.1.2 Regimen 2A (Weekly x 3)

- Course 1, Day 1 and Day 8: pre-dose, 15 min, 30 min, 60 min, 90 min and 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, and 24 hr post-dose

9.2.1.3 Regimen 2B (Days 1, 4, 8, 11, 15, and 18 of a 28-day course)

- Course 1, Day 1: pre-dose, 15 min, 30 min, 60 min, 90 min and 2 hr, 3 hr, 4 hr, 6 hr, and 8 hr post-dose

9.2.1.4 10-Day Regimen (Dose Expansion, Treatment-naïve AML Subjects)

- Course 1, Day 1: pre-dose, 15 min, 30 min, 60 min, 90 min and 2 hr, 3 hr, 4 hr, 6 hr, and 8 hr post-dose
- Course 1, Day 12: pre-dose and 2 hr (±30 min) post-dose

Sampling windows are up to 10% of protocol specified timepoint but no more than 1 hour. Further information regarding the collection, processing, labeling and shipping of PK samples will be detailed in the SGI-110-01 Laboratory Manual.

9.2.2 On Study Treatment Assessments and Procedures

Note: The following text in Section 9.2.2.1 (Regimen 1 and Dose Expansion), Section 9.2.2.2 (Regimen 2A), Section 9.2.2.3 (Regimen 2B) and Section 9.2.2.4 (the 10-day schedule) represents Course 1 assessments and procedures. Table 2 shows all assessments and procedures for ≥ Course 2. Further urinalysis testing after Screening is only as needed at the Investigator's discretion.

9.2.2.1 Regimen 1 and Dose Expansion

Five daily doses of SGI-110 administered on Days 1–5 constitutes one course of SGI-110 study treatment.

Day 1

- Complete physical examination. This test does not need to be repeated if it was done up to 4 days before the first dose of SGI-110.
- Vital signs
- ECOG Performance Status
- 12-lead ECG (ECG does not need to be repeated if it was done up to 4 days before the first dose of SGI-110.)
- Weight and BSA calculation (see Appendix 3; use height from Screening)
- Sample collection for clinical laboratory tests, including:

- Hematology: complete blood count (CBC) with manual differential and platelet counts. (Hematology evaluation does not need to be repeated if it was done up to 4 days before the first dose of SGI-110.)

- Chemistries: glucose, calcium, magnesium, albumin, total protein, sodium, potassium, CO2, chloride, blood urea nitrogen, creatinine, lactate dehydrogenase, alkaline phosphatase, ALT, AST, and total bilirubin. (Chemistry evaluation does not need to be repeated if it was done up to 4 days before the first dose of SGI-110.)

- Epigenetics: Pre-dose AND pre-dose at Day 1 of Course 2.

- Buccal swab before first dose of study drug.

- Pharmacogenetic markers: Includes but not limited to hENT-1 and -2, dCK, and cytidine deaminase pre-dose at Course 1 only

Days 2–5

- Symptom-directed physical examination

- Vital signs

Day 8 (±2 days), Day 15 (±2 days), Day 22 (±2 days)

- Sample collection for clinical laboratory tests, including:

  - Hematology: complete blood count (CBC) with manual differential and platelet counts.

  - Epigenetics: pre-dose Course 1 only

Day 28 (At the end of every course)

- Response assessment

At Every Protocol Scheduled Study Center Visit

- Documentation of all concomitant medications and procedures within 14 days prior to the start of study drug administration through 30 days after the last dose of study treatment.

- Documentation of all transfusions from 28 days prior to the start of study drug administration through 30 days after the last dose of study treatment.

- Documentation of all study-procedure related AEs from the time of informed consent and then treatment-emergent AEs after the start of study drug administration (Course 1, Day 1) through 30 days after the last dose of study treatment.

9.2.2.2 Regimen 2A

Three weekly courses administered once weekly on Days 1, 8, 15 constitute one course of SGI-110 study treatment.

Day 1

- Complete physical examination. This test does not need to be repeated if it was done up to 4 days before the first dose of SGI-110.
- Vital signs
- ECOG Performance Status
- 12-lead ECG (ECG does not need to be repeated if it was done up to 4 days before the first dose of SGI-110.)
- Weight and BSA calculation (see Appendix 3; use height from Screening)
- Sample collection for clinical laboratory tests, including:
    - Hematology: complete blood count (CBC) with manual differential and platelet counts. (Hematology evaluation does not need to be repeated if it was done up to 4 days before the first dose of SGI-110.)
    - Chemistries: glucose, calcium, magnesium, albumin, total protein, sodium, potassium, CO2, chloride, blood urea nitrogen, creatinine, lactate dehydrogenase, alkaline phosphatase, ALT, AST, and total bilirubin. (Chemistry evaluation does not need to be repeated if it was done up to 4 days before the first dose of SGI-110.)
    - Epigenetics: Pre-dose AND pre-dose at Day 1 of Course 2.
    - Buccal swab before first dose of study drug.
    - Pharmacogenetic markers: Includes but not limited to hENT-1 and -2, dCK, and cytidine deaminase pre-dose at Course 1 only

Day 8 (±2 days), Day 15 (±2 days)

- Symptom-directed physical examination
- Vital signs
- Sample collection for clinical laboratory tests, including:

- Hematology: complete blood count (CBC) with manual differential and platelet counts.
- Epigenetics: pre-dose Course 1 only

Day 22 (± 2 days)

- Sample collection for clinical laboratory tests, including:
  - Hematology: complete blood count (CBC) with manual differential and platelet counts.
  - Epigenetics: pre-dose Course 1 only

Day 28 (At the end of every course)

- Response assessment

At Every Protocol Scheduled Study Center Visit

- Documentation of all concomitant medications and procedures within 14 days prior to the start of study drug administration through 30 days after the last dose of study treatment.
- Documentation of all transfusions from 28 days prior to the start of study drug administration through 30 days after the last dose of study treatment.
- Documentation of all study-procedure related AEs from the time of informed consent and then treatment-emergent AEs after the start of study drug administration (Course 1, Day 1) through 30 days after the last dose of study treatment.

9.2.2.3 Regimen 2B

Three weekly courses administered twice weekly on Days 1, 4, 8, 11, 15, and 18 constitute one course of SGI-110 study treatment.

Day 1

- Complete physical examination. This test does not need to be repeated if it was done up to 4 days before the first dose of SGI-110.
- Vital signs
- ECOG Performance Status
- 12-lead ECG (ECG does not need to be repeated if it was done up to 4 days before the first dose of SGI-110.)

- Weight and BSA calculation (see Appendix 3; use height from Screening)
- Sample collection for clinical laboratory tests, including:
    - Hematology: complete blood count (CBC) with manual differential and platelet counts. (Hematology evaluation does not need to be repeated if it was done up to 4 days before the first dose of SGI-110.)
    - Chemistries: glucose, calcium, magnesium, albumin, total protein, sodium, potassium, CO2, chloride, blood urea nitrogen, creatinine, lactate dehydrogenase, alkaline phosphatase, ALT, AST, and total bilirubin. (Chemistry evaluation does not need to be repeated if it was done up to 4 days before the first dose of SGI-110.)
    - Epigenetics: Pre-dose AND pre-dose at Day 1 of Course 2.
    - Buccal swab before first dose of study drug.
    - Pharmacogenetic markers: Includes but not limited to hENT-1 and -2, dCK, and cytidine deaminase pre-dose at Course 1 only

Day 4, Day 11, Day 18 (±1 day each)

- Symptom-directed physical examination
- Vital signs

Day 8, Day 15 (±2 days each)

- Symptom-directed physical examination
- Vital signs
- Hematology: complete blood count (CBC) with manual differential and platelet counts.
- Epigenetics: pre-dose Course 1 only

Day 22 (± 2 days)

- Sample collection for clinical laboratory tests, including:
    - Hematology: complete blood count (CBC) with manual differential and platelet counts.
    - Epigenetics: pre-dose Course 1 only

Day 28 (At the end of every course)

- Response assessment

At Every Protocol Scheduled Study Center Visit

- Documentation of all concomitant medications and procedures within 14 days prior to the start of study drug administration through 30 days after the last dose of study treatment.
- Documentation of all transfusions from 28 days prior to the start of study drug administration through 30 days after the last dose of study treatment.
- Documentation of all study-procedure related AEs from the time of informed consent and then treatment-emergent AEs after the start of study drug administration (Course 1, Day 1) through 30 days after the last dose of study treatment.

9.2.2.4 The 10-day Schedule

Ten daily doses of SGI-110 administered on Days 1-5 and 8-12 (Monday through Friday each week for 2 weeks) constitute one course of SGI-110 study treatment.

Day 1

- Complete physical examination. This test does not need to be repeated if it was done up to 4 days before the first dose of SGI-110.
- Vital signs
- ECOG Performance Status
- 12-lead ECG (ECG does not need to be repeated if it was done up to 4 days before the first dose of SGI-110.)
- Weight and BSA calculation (see Appendix 3; use height from Screening)
- Sample collection for clinical laboratory tests, including:
    - Hematology: complete blood count (CBC) with manual differential and platelet counts. (Hematology evaluation does not need to be repeated if it was done up to 4 days before the first dose of SGI-110.)
    - Chemistries: glucose, calcium, magnesium, albumin, total protein, sodium, potassium, CO2, chloride, blood urea nitrogen, creatinine, lactate dehydrogenase, alkaline phosphatase, ALT, AST, and total bilirubin. (Chemistry evaluation does not need to be repeated if it was done up to 4 days before the first dose of SGI-110.)
    - Epigenetics: Pre-dose AND pre-dose at Day 1 of Course 2.

- Buccal swab before first dose of study drug.
- Pharmacogenetic markers: Includes but not limited to hENT-1 and -2, dCK, and cytidine deaminase pre-dose at Course 1 only

Days 2-5

- Symptom-directed physical examination
- Vital signs

Day 8

- Symptom-directed physical examination
- Vital signs
- Sample collection for clinical laboratory tests, including:
  - Hematology: complete blood count (CBC) with manual differential and platelet counts.
  - Epigenetics: pre-dose Course 1 only

Days 9-12

- Symptom-directed physical examination
- Vital signs

Day 15, Day 22 (±2 days each)

- Sample collection for clinical laboratory tests, including:
  - Hematology: complete blood count (CBC) with manual differential and platelet counts.
  - Epigenetics: pre-dose Course 1 only

Day 28 (At the end of every course)

- Response assessment

At Every Protocol Scheduled Study Center Visit

- Documentation of all concomitant medications and procedures within 14 days prior to the start of study drug administration through 30 days after the last dose of study treatment.

- Documentation of all transfusions from 28 days prior to the start of study drug administration through 30 days after the last dose of study treatment.

- Documentation of all study-procedure related AEs from the time of informed consent and then treatment-emergent AEs after the start of study drug administration (Course 1, Day 1) through 30 days after the last dose of study treatment.

9.3 Termination–All Subjects (Regimen 1, Regimen 2A, Regimen 2B, Dose Expansion and 10-Day Schedule)

The Termination Visit is conducted within 5 days of the subject terminating the study. The following evaluations are to be performed and laboratory samples are to be collected:

- Complete physical examination

- Vital signs

- ECOG Performance Status

- Sample collection for clinical laboratory tests, including:

  - Hematology: complete blood count (CBC) with manual differential and platelet counts.

  - Chemistries: glucose, calcium, magnesium, albumin, total protein, sodium, potassium, CO2, chloride, blood urea nitrogen, creatinine, lactate dehydrogenase, alkaline phosphatase, ALT, AST, and total bilirubin.

  - Serum pregnancy test: for female subjects of child-bearing potential only.

- Concomitant medications and procedures (see above)

- Transfusions (see above)

- AEs (see above)

- Response assessment

9.4 30-Day or Safety Follow-Up – All Subjects (Regimen 1, Regimen 2A, Regimen 2B, Dose Expansion and 10-Day Schedule)

Each subject should be followed, to document the occurrence of any new events, for at least 30 (+5) days after his or her last dose of SGI-110 (ie, the "safety follow-up visit") or as long as any significant toxicity has not resolved to a clinically acceptable or stable resolution (see Section 10.0). Subjects who withdraw consent should still be encouraged to complete the early

termination and safety follow up visits. Table 2 describes the procedures required for the early termination and 30-day safety follow-up visits.

- Symptom directed physical examination
- Vital signs
- ECOG Performance Status
- Concomitant medications and procedures (see above)
- Transfusions (see above)
- AEs (see above)

9.5 Conversion to AML (MDS subjects); and Survival Follow Up – All Subjects (Regimen 1, Regimen 2A, Regimen 2B, Dose Expansion and 10-Day Schedule)

- At the end of every course during treatment. Every 3 months after stopping study treatment.

9.6 Missed Evaluations

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the investigator's opinion, medically unnecessary because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

9.7 Response Criteria

All responses will be documented. The following is a summary of the response criteria, the detailed criteria based on the published references will be further described in the statistical analysis plan to guide the analysis.

9.7.1 MDS

The response criterion for evaluation of MDS is based on the International Working Group criteria published by Cheson *et al*, in 2006 [2].

Table 3: IWG 2006 MDS Response Criteria

Complete Response (CR): the following for 4 weeks		
Peripheral: Marrow:	normal peripheral counts with persistent granulocyte count ≥ 1.0 X 10^9/L, platelet count ≥ 100 X 10^9/L normal bone marrow with persistent marrow blasts ≤ 5%; persistent dysplasia will be noted	
Partial Response (PR): the following for 4 weeks		
Peripheral: Marrow:	normal peripheral counts with granulocyte count ≥ 1.0 X 10^9/L and platelet count ≥ 100 X 10^9/L normal bone marrow with marrow blasts > 5% but were reduced by 50% or more	
Marrow Complete Response (mCR): the following for 4 weeks		
Reduction of bone marrow blasts to ≤ 5% without normalization of peripheral counts		
Hematological Improvement (HI): lasts at least 8 weeks*		
Erythroid Response (HI-E):	*Major Response:*	hemoglobin increase ≥ 1.5 g/dL or RBC transfusion independence
Platelet Response (HI-P):	*Major Response:*	absolute increase of platelet count from <20 to > 20 X 10^9/L and by at least 100%, or if more than 20 X 10^9/L, by an absolute increase of at least 30 X 10^9/L
Neutrophil Response (HI-N):	*Major Response:*	granulocyte increase ≥ 100%, and by an absolute increase ≥ 0.5 X 10^9/L

*Abnormal baseline counts were the averages of at least two measurements over at least one week prior to therapy, not influenced by transfusions.

Reference: [2].

9.7.2 AML

The response criteria for AML will be based on revised recommendation of the International Working Group published by Cheson *et al*, in 2003 [3].

Table 4: AML

Response	Peripheral Blood	Bone Marrow
CR	ANC > 1.0 x 10^9/L, Platelets ≥ 100 x 10^9/L, no blasts, independence from red cell and platelet transfusions over the past week	<5% blasts
CRp	ANC > 1.0 x 10^9/L, Platelets < 100 x 10^9/L, no blasts, independence from red cell transfusions over the past week	<5% blasts
CRi	ANC < 1.0 x 10^9/L, no blasts	<5% blasts
PR	ANC > 1.0 x 10^9/L, Platelets ≥ 100 x 10^9/L, no blasts	Decrease of ≥ 50% in blasts to level of 5% to 25%

ANC = absolute neutrophil count; CR = complete remission; CRp = complete remission with incomplete platelet recovery; CRi = CR with incomplete blood count recovery; PR = partial remission

Reference: [3]

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 administration of a medicinal product, whether or not considered related to the medicinal product 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.

If there are specific AEs that are always part of disease progression, these do not need to be reported as AEs or serious adverse events (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.

An AE 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 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.

10.2 Adverse Event Reporting and Descriptions

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, will be noted in the AEs section of the subject's CRF, in the source document, and if applicable, recorded on the SAE form.

New AEs will be recorded from the start of study treatment till 30 days after last treatment administration. Screening procedure-related AEs that occur before the start of study treatment will also be recorded. 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."

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

For any change in laboratory results, vital signs, physical examination, radiologic exam or ECG measurements that arises after treatment, the Investigator will decide if the finding or result is clinically significant and will determine if it is necessary to repeat the evaluation. If the evaluation is judged to be clinically significant, it must be recorded as an AE, and if applicable, reported as an SAE. Clinically significant laboratory findings include any lab for which a therapeutic intervention is initiated to correct the abnormality.

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

Definitions found in the CTCAE v4.0 will be used for grading the severity (intensity) of AEs. The CTCAE v4.0 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 v4.0, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

10.2.2 Relationship to Study Treatment (Suspected Adverse Reactions)

All AEs/SAEs must be assessed for relationship to study drug or if applicable, to study procedure.

If an AE/SAE occurs before the initiation of the investigational product, the Investigator will assess the relationship of the AE to the specific study screening activity (e.g., screening laboratory test).

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 (e.g., 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 (e.g., acute myocardial infarction in a young woman), • An aggregate analysis of specific events observed in a clinical trial (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 than in a concurrent or historical control group.
Not related (Not Suspected)	Adverse events that do not meet the above criteria.

10.2.3 Pregnancy and Abortion

Report any pregnancy that occurs in a subject or subject's partner from the time of consent to 60 days after the last dose of study drug. Record any occurrence of pregnancy on the Pregnancy Report Form Part I and fax to Astex Pharmaceuticals Drug Safety within 24 hours of learning of

the event. After the birth of the baby, additional information on the baby will be collected until the baby is 2 years old by completing the Pregnancy Report Form Part II. Abortion and the reason for it, whether therapeutic, elective or spontaneous, will be reported as an SAE.

A subject must immediately inform the investigator if the subject or subject's partner becomes pregnant from the time of consent to 60 days after the last dose of study drug. Any female subjects receiving SGI-110 who become pregnant must immediately discontinue study drug. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

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 following the discontinuation of study medication. Deaths and SAEs occurring after the 30-day safety follow-up period AND considered related to study drug or study procedures must also be reported.

All SAEs (initial and follow-up information) will be reported on an SAE form and faxed 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	
US and Canada Local Fax:	(925) 551-3226
US and Canada Toll Free Fax:	(800) 576-6568
Email:	drugsafety@astx.com

All deaths should be reported with the primary cause of death as the AE and SAE term, as death is the outcome of the event, not the event itself. If an autopsy was performed, the primary cause of death on the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to Astex Pharmaceuticals Drug Safety, or designee, as outlined above.

If study drug is discontinued, temporarily suspended or dose reduced because of an SAE, this information must be included in the SAE report.

An SAE may qualify for mandatory expedited reporting to regulatory authorities if the SAE is attributable to the study drug or study regimen and is considered unexpected (ie, not defined as expected in the current Investigator's Brochure, or clinical study protocol). In this case, Astex Pharmaceuticals Drug Safety or Designee will forward a formal notification describing the SAE to all investigators. Each investigator must then notify his or her IRB or IEC of the SAE as required by local regulatory authorities and in accordance with IRB or IEC policy.

10.4 Follow-up for Adverse Events

All AEs and SAEs that are encountered during the protocol-specified AE reporting period should be followed to resolution, until the investigator assesses the subject as stable, the event is following a clinically expected outcome, or the subject is lost to follow-up or withdraws consent.

11.0 STATISTICAL CONSIDERATIONS

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

Additional details of the analysis will be provided in the statistical analysis plan and/or the clinical study report. This may include details of missing and, if applicable, unused and spurious data. Deviations from the statistical plan will be reported in the clinical study report.

11.1 Sample Size

No formal statistical tests of hypotheses will be performed comparing SGI-110 to control treatment, as is characteristic in Phase 1 trials. The number of subjects enrolled during the Dose Escalation Segment of the study is based on response (DNA hypomethylation, gene expression and/or occurrence of dose limiting toxicities) to SGI-110. At the recommended Dose Expansion Segment dose(s) and schedule(s), a minimum of 30 subjects will be enrolled in each of the following 6 subgroups: 1) HMA treatment-naïve MDS (including CMML); 2) relapsed/refractory intermediate-2 or high-risk MDS (including CMML); 3) relapsed/refractory AML treated with the 5-day regimen; 4) relapsed/refractory AML treated with the 10-day regimen; 5) treatment-naïve elderly AML treated with the 5-day regimen; and 6) treatment-naïve elderly AML treated with the 10-day regimen. The sample size of 30 subjects in each subgroup was selected so that if no responses were observed it will be concluded, with 95% confidence, that the response rate in that subgroup is <10% and therefore not worthy of further development. The SRC for a particular subgroup, where the most number of responses are observed, may increase the number of subjects up to 50 subjects per subgroup to have a better assessment of efficacy in that subgroup.

11.2 Data Sets to be Analyzed

11.2.1 Efficacy and Safety Data Set

The efficacy and safety data sets will include data from all subjects who receive at least one dose of study drug. All data will be included and no subjects excluded because of protocol violations. Subjects treated in the Dose Escalation Segment may be analyzed together with subjects treated at the same dose and dose regimen in the Dose Expansion Segment.

11.2.2 Pharmacokinetic and Pharmacodynamic

The pharmacokinetic (PK) data set will include all available plasma concentrations and PK parameters for SGI-110 and decitabine for subjects who have received test article assuming available PK data is evaluable.

Descriptive statistics including mean and standard deviation will be summarized SGI-110 and decitabine plasma concentrations at each planned time point. Descriptive statistics will also be summarized for PK parameters of SGI-110 and decitabine.

Subjects will be included in the pharmacodynamic analyses if they have provided blood samples for the analysis of DNA global methylation (LINE-1) and gene specific re-expression.

11.3 Schedule of Analyses

Ad hoc presentation and/or analyses of safety, efficacy, and PK data will be regularly performed for review by the SRC for the purpose of guiding decisions such as dose escalation, de-escalation, change in cohort size, determination of MTD or BED. Final analyses will be performed at the end of the study when all patients had received at least one course of therapy.

11.4 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. Summaries will be provided separately for each treatment group.

11.5 Efficacy Variables and Analyses

Response rates and 95% confidence intervals will be estimated within dose level, and for the dose expansion segment by regimen.

MDS response criteria (see Section 9.7.1) require confirmation of abnormal baseline laboratory test results with a repeat assessment. The baseline value, against which hematological improvement is measured, being the average of at least two measurements over at least one week prior to therapy. The schedule of events in this protocol does not mandate repeating baseline tests if baseline is within 4 days of initiation of therapy. In this case, the single baseline result will be used to determine HI according to IWG criteria.

Within each regimen, assessments of hypomethylation will be plotted against SGI-110 dose to determine the dose level at which hypomethylation plateaus, where plateau is defined as absence of meaningful increase in hypomethylation over three consecutive dose levels. If a plateau in hypomethylation is observed before reaching the MTD, then the minimum BED will be defined as the lowest SGI-110 dose level of the plateau.

For subjects entering the study with MDS, time to AML or death is the number of days from the day the subject received the first dose of SGI-110 to the date of death or the date of MDS progression to AML defined by ≥20% blasts in bone marrow or peripheral blood.

Overall survival is the number of days from the day the subject received the first dose of SGI-110 to the date of death (regardless of cause).

Subjects withdrawing from the study prior to reaching a time-to-event endpoint will be contacted periodically to obtain the endpoint date (see Table 2 Section 9.0). Median overall survival and time to AML or death will be estimated by Kaplan-Meier analysis. Survival time and time to AML or death will be censored on the last date of contact if a subject is lost to follow-up prior to reaching a time-to-event endpoint.

11.6 Safety Variables and Analyses

Within each dosing regimen, SGI-110 MTD will be defined as the largest dose for which fewer than 33% of subjects experience a DLT during the first course of administration. Safety will be assessed by subject reported and Investigator observed AEs along with physical examination, clinical laboratory tests (hematology, chemistries, and urinalysis), and serial ECGs. Safety variables will be tabulated and presented for all subjects who receive any amount of SGI-110. Exposure to SGI-110 and reasons for discontinuation will be tabulated. Summarization will focus on rates of treatment emergent adverse events by MedDRA System Organ Class and Preferred Term; by CTC grades, and reasons for discontinuation of SGI-110.

11.7 Pharmacokinetic Variables and Analyses

PK parameters will be derived for each subject using non-compartmental approach. Descriptive statistics including mean, SD, median and range for PK parameters for SGI-110 and decitabine will be summarized by cohort and regimen. PK dose proportionality will be tested using linear regression between dose and dose-adjusted parameter estimates; correlation of PK to PD will be assessed.

11.8 Interim Analysis

There will be no interim analyses in this study.

11.9 Procedures for Handling Missing, Unused, and Spurious Data

All available efficacy and safety data will be included in data listings and tabulations. No imputation of values for missing data will be performed. Subjects lost to follow-up will be included in statistical analyses to the point of their last evaluation. All study data will be examined using standard data management operating procedures.

12.0 ESTIMATED DURATION OF THE STUDY

It is estimated that the Dose Escalation Segment will take approximately 12-18 months to complete enrollment for an estimate of four to eight cohorts per regimen to determine the optimal BED or MTD. The Dose Expansion Segment is expected to have an additional 12-18 month enrollment period.

13.0 STUDY COMPLIANCE AND ETHICAL CONSIDERATIONS

13.1 Compliance Statement

The study will be conducted in accordance with the ICH GCP guidelines; US 21 CFR Parts 50, 54, 56, and 312; and the principles enunciated in the Declaration of Helsinki.

13.2 Informed Consent

The informed consent forms used for the study must comply with the Declaration of Helsinki, federal regulations US 21 CFR Parts 50, and ICH GCP guidelines. An 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. Other elements of the informed consent process may be delegated by the Investigator. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Documentation of the discussion and the date of informed consent must be recorded in the source documentation. Subjects must give informed consent in writing.

The informed consent process must be conducted, and the form must be signed, before the subject undergoes any screening procedures that are performed solely for the purpose of determining eligibility for the study.

13.3 Institutional Review Board, Ethics Committee, or Research Ethics Board (IRB)

The protocol, protocol amendments (as specified by the IRB), and the informed consent form for the proposed study, along with any other documents required by the center's IRB must be submitted by the Investigator to the center's duly constituted IRB for review and approval. The Investigator must also ensure that the IRB 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 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's Responsibilities

Astex Pharmaceuticals retains the right to terminate the study and remove all study materials from a study site at any time. Specific circumstances that may precipitate such termination are:

- 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 and maintain adequate study records
- Inaccurate, incomplete and/or late data recording on a recurrent basis
- The incidence and/or severity of AEs in this or other studies indicating a potential health hazard caused by the study treatment

14.1.1 Study Supplies

The Sponsor will supply sufficient quantities of the following materials to each clinical center:

- Study drug as described in Section 7.0
- Investigator's Brochure (IB) for study drug

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 prior to enrollment of the first subject at each study center. Each study center will be provided with information regarding GCP and regulations specific to the conduct of clinical studies.

14.1.3 Ongoing Communication of Safety Information During the Study

The Sponsor will provide the Investigator with documentation of SAEs, from all study centers, reported to regulatory authorities (reportable SAEs) during the conduct of the study. The Investigator must forward this documentation to the IRB, as described in Section 10.3.1.

The Sponsor will also notify the Investigator about any other safety findings that could affect the safety of subjects, affect the conduct of the study, or alter the IRB's opinion about continuation of the study.

14.1.4 Study Monitoring

The study will be monitored by representatives of Astex Pharmaceuticals. Routine monitoring visits will be conducted to:

- Assure compliance with the study protocol.
- Verify that the informed consent process was conducted before initiation of any screening procedures that are performed solely for the purpose of determining eligibility for the study and prior to the provision of study medication.
- Verify that the protocol, protocol amendments, and safety information are submitted to the IRBs in a timely manner.
- Review the CRFs and source documents to ensure that reported study data are accurate, complete, and verifiable from source documents.
- Verify that the investigational products are stored properly and under the proper conditions, that they are in sufficient supply, and that receipt, use, and return of investigational products 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.

In addition, periodic monitoring will be conducted to ensure that adequate records of clinical study supplies are maintained.

14.1.5 Records Retention

The Sponsor must retain all documentation pertaining to the study according to Astex Pharmaceuticals standard operating procedures.

14.2 Investigator's 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 Investigational Study Drug Accountability

An initial supply of SGI-110 and diluent vials will be shipped to each site's pharmacy when all the initiation documents, including IRB approvals and IRB approved ICF, have been received and reviewed by Astex Pharmaceuticals and upon activation of the site by Astex Pharmaceuticals. Thereafter, it is the responsibility of the trial pharmacist to order a resupply.

SGI-110 must be kept in a locked limited access room. The study drug must not be used outside the context of the protocol. Under no circumstances should the investigator or other site personnel supply SGI-110 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. SGI-110 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.

All SGI-110 supplies and associated documentation will be regularly reviewed and verified by the monitor.

14.2.3 Reporting and Recording of Study Data

Data will be captured and compiled using procedures developed by the Sponsor or their representatives. All requested study data must be recorded clearly on the CRF and other study forms as required. An explanation should be provided for all missing data. Only individuals who are identified on the Study Personnel Identification List may enter or correct data in the CRF. Incomplete or inconsistent data on the CRFs will result in data queries that require resolution by the Investigator.

The protocol, informed consent form, protocol amendments, safety information, and other required documents must be submitted to the IRB in a timely manner, as described in Section 10.3.1 (for safety information) and Section 13.3 (for other documents).

14.3 Source Documentation

The Investigator must maintain adequate and accurate source documents upon which CRFs for each subject are based. They are to be separate and distinct from CRFs, except for cases in which the Sponsor has predetermined that direct data entry into specified pages of the subject's CRF 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). The date of informed consent must be recorded in the source documentation.

- The subject's medical history prior to participation in the study.

- The subject's basic identifying information, such as demographics, that links the subject's source documents with the CRFs.
- 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.

14.3.1 Study Drugs

The Investigator is responsible for ensuring the study drugs are administered or dispensed only to subjects enrolled in the study. An accurate accounting of the study drugs and investigational devices must be maintained using a separate form. These records must show dates, lot numbers, and quantities received, dispensed, and returned. The Investigator will ensure that any used and unused vials of study drug and other study material will be destroyed or returned to the Sponsor on completion of the study.

14.3.2 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. Mandatory documentation includes copies of study protocols and amendments, each FDA Form 1572, IRB or IEC approval letters, signed ICFs, drug accountability records, SAE forms transmitted to Astex Pharmaceuticals, subject files (source documentation) that substantiate entries in CRFs, 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.

Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution, or private practice. The Investigator must inform the Sponsor immediately if any documents are to be destroyed, to be transferred to a different facility, or to be transferred to a different owner.

14.4 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 sites at the time of study initiation.

14.5 Protocol Amendments

Astex Pharmaceuticals will initiate any other change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB or IEC together with, if applicable, a revised model ICF. If the change in any way increases the risk to the subject or changes the scope of the study, then written documentation of IRB or IEC approval must be received by Astex Pharmaceuticals before the amendment may take effect. Additionally under this circumstance, information on the increased risk and/or change in scope 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 trial.

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 participation of the Sponsor. The Principal Investigators and the Sponsor may propose appropriate scientific manuscripts or abstracts from the study data. All proposed publications must be reviewed and commented on by the Sponsor before submission for publication. The detailed procedures for the review of publications is 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).

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APPENDICES

APPENDIX 1: ECOG AND KARNOFSKY PERFORMANCE STATUS

Score	ECOG Description	Score	Karnofsky Description
0	Fully active, able to carry on all predisease performance without restriction	100	Normal: no complaints, no evidence of disease
		90	Able to carry on normal activity; minor symptoms
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	80	Normal activity with effort; some symptoms
		70	Cares for self; unable to carry on normal activities
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	60	Requires occasional assistance; cares for most needs
		50	Requires considerable assistance and frequent care
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled: requires special care and assistance
		30	Severely disabled: hospitalized but death not imminent
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair	20	Very sick: active supportive care needed
		10	Moribund: fatal processes are progressing rapidly
5	Dead	0	Dead

Sources:

ECOG Performance Status — http://www.ecog.org/general/perf_stat.html (accessed August 30, 2007)

Karnofsky Performance Status — http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/neurology/braintumor/table3.htm (accessed February 11, 2008)

APPENDIX 2: NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (4.0)

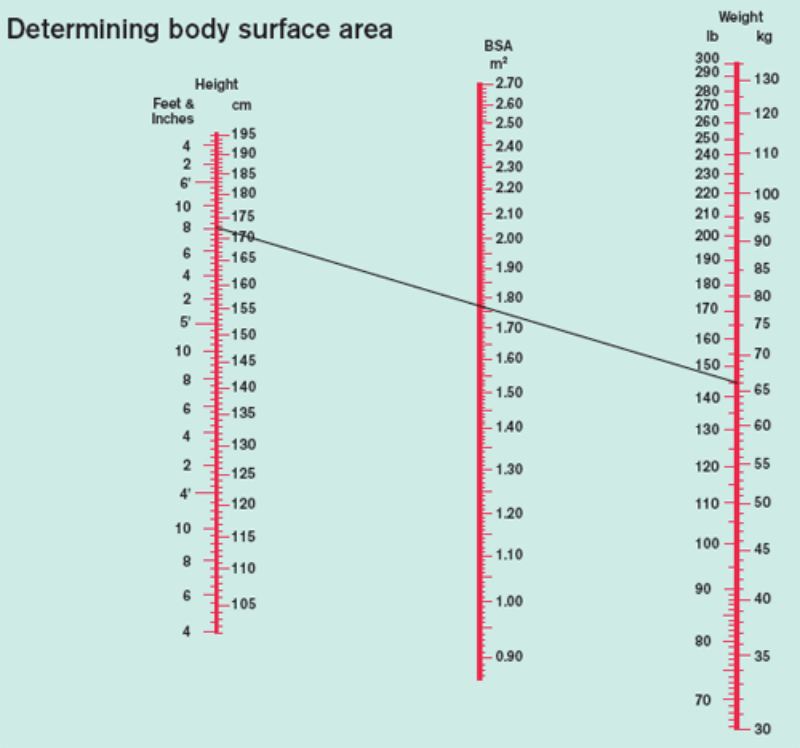
In the present study, adverse events and/or adverse drug reactions will be recorded to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

The NCI CTCAE criteria can be viewed electronically at the following web link:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (accessed 24 March 2010)

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

APPENDIX 3: BSA NOMOGRAM



Source: www.epgonline.org/page.cfm/pageid/794

This BSA nomogram is an example to calculate BSA. The institutional standard to calculate BSA is acceptable.

APPENDIX 4: SUMMARY OF CHANGES, AMENDMENT 3

Protocol: SGI-110-01

Amendment Date: 07 September 2012

Amendment 3 introduces the addition of a 10-day treatment schedule for SGI-110 in the Dose Expansion Segment for the treatment of up to 50 subjects with refractory/relapsed AML.

Rationale for Amendment 3:

Based on emerging favorable data from using decitabine 10-day regimen in AML, and since SGI-110 delivers decitabine as its active ingredient, it is hypothesized that a 10-day treatment schedule of SGI-110 may improve response in subjects with relapsed/refractory AML who have no other approved treatment options. Since SGI-110 given at 125 mg/m^2 dailyx5 was tolerated by AML subjects in the Dose Escalation Segment, it was agreed by the SRC to study the 10-day dosing schedule of SGI-110 only in relapsed/refractory AML subjects using the dose of 60 mg/m^2 dailyx10. This amounts to a total dose per course of 600 mg/m^2 which is similar to the total highest dose tested in the Dose Escalation Segment (125 mg/m^2 dailyx5 amounts to a total dose per course of 625 mg/m^2).

A few other clarifications, corrections and administrative changes were also made.

Summary of Changes:

A. Main Change:

1. Introduced the 10-day treatment schedule in the Dose Expansion Segment for relapsed/refractory AML subjects. **(Section 2.2, Section 4.1, Section 7.2, Section 9)**

B. Other minor or administrative changes for clarifications, corrections, or update to the study conduct:

1. Documentation of the doses selected for randomization (60 mg/m^2 and 90 mg/m^2 dailyx5) by the Safety Review Committee (SRC) for the Dose Expansion Segment. **(Section 2.2, Section 4.1, Section 5.1)**

2. A new section summarizing the clinical data (demographics, PK, PD, safety and response) obtained in the Dose Escalation Segment to date of the study was included. **(Section 1.6)**

3. The risks of SGI-110 based on early clinical data was updated. **(Section 1.7.3)**

4. The number of subjects for PK assessment in the Dose Expansion Segment of the study was clarified to be 10 AML subjects and 10 MDS subjects. Few PK time points were removed from the dose expansion segment: Course 1, Day 1 24-hr post-dose; Course 1, Days 2-4; and l Course 1, Day 5 pre-dose PK sampling time points are no longer required based on PK data from the Dose Escalation Segment. **(Section 4.1, Section 9.2)**

5. Documentation of the SRC to allow up to 50 relapsed/refractory AML subjects to be randomized to the 2 doses of the 5-daily regimen. This increase was already permissible in the prior protocol version. **(Section 5.1)**

6. Clarifying text that Regimen 2B enrollment was not randomized and the disease subtype stratification in the Dose Expansion Segment was added. **(Section 6.1)**

7. The criteria for adjusting of withholding study drug dosing section was updated with guidance for the Dose Expansion Segment in MDS and AML subjects. **(Section 7.3)**

8. The AML response criteria table was updated to clarify the time period required for transfusion-independence. **(Section 9.7.2)**

9. The Medical Monitor for the study was changed from Dr. Robert Corringham, MD to Dr. Lynne Bui, MD and the Study Statistician for the study was changed from Dr. Gil Fine, PhD to Dr. Mojtaba Noursalehi, PhD.

All text changes that were made to the protocol for this amendment are shown in the redlined version.

APPENDIX 5: SUMMARY OF CHANGES, AMENDMENT 4

Protocol: SGI-110-01

Amendment Date: 15 March 2013

Amendment 4 adds enrollment of intermediate-2 or high-risk MDS subjects (including chronic myelomonocytic leukemia [CMML]) who have relapsed or are refractory to prior hypomethylating agent (HMA) treatment to the Dose Expansion Segment.

Rationale for Amendment 4:

Subjects with advanced MDS relapsed to prior treatment with HMAs have limited treatment options and low rates of survival. Based on emerging favorable response data from relapsed MDS subjects in the Dose Escalation Segment, it is important to continue to study those subjects in the Dose Expansion Segment.

Summary of Changes:

A. Main Change:

1. Added text that intermediate-2 or high-risk MDS subjects (including CMML) relapsed or refractory to prior HMA treatment will be enrolled in the Dose Expansion Segment. **(Sections 4.1 and 4.2, Sections 5.1-5.3, Section 6.1, Section 7.2, Section 11.1)**

B. Other minor or administrative changes for clarifications, corrections, or update to the study conduct:

1. Added cross-reference to Investigator's Brochure for most updated clinical and safety data for SGI-110. **(Section 1.6, Section 1.7.3)**

2. Clarified that 4 disease subgroup populations will be studied in the Dose Expansion Segment. **(Sections 4.1 and 4.2, Sections 5.1, Section 6.1, Section 7.2, Section 11.1)**

3. Clarified that the study is enrolling "HMA" treatment-naïve MDS subjects in the Dose Expansion Segment since MDS subjects who received supportive treatment other than HMAs are still eligible. **(Section 5.2)**

4. Added 4th subcategory of treatment-naïve elderly AML subjects eligible for participation in the study: subjects with poor performance status, ECOG, of 2. **(Section 5.2)**

5. Clarified a criterion for subject withdrawal from the study as those subjects who have a DLT that does not improve to baseline or to ≤ Grade 1 "for 4 weeks or more". **(Section 5.4)**

6. Clarified the disease type and prior treatment stratification of the study. **(Section 6.1)**

7. Replaced statement that reconstituted SGI-110 is stable under refrigerated conditions for 30 days to "at least 8 days" to be consistent with the Pharmacy Manual. **(Section 7.1.4)**

8. Corrected inconsistency about withholding and restarting SGI-110 in the event of a DLT that has not resolved to "baseline" or ≤ Grade 1. **(Section 7.3)**

9. Clarified that hematopoietic growth factors can be used if judged clinically necessary by the investigator. **(Section 7.4.2)**

10. Deleted a few unnecessary tests/assessments in Schedule of Events table and relevant sections in the protocol. 1) 12-lead ECG will be conducted at Screening and Day 1 of every course, and now only as needed after Course 4, at the investigator's discretion, 2) urinalysis will now be conducted at Screening, and only as needed thereafter at the investigator's discretion, 3) deleted Screening and Termination Visit Epigenetics/CTA test, and 4) deleted buccal swab at Screening. We also added a requirement to confirm response with bone marrow aspirates at least every other cycle for those subjects whose peripheral counts suggest that they are responders to ensure consistent assessment of responses across the different clinical sites. **(Section 9.0)**

11. Clarified that the details of the response criteria in the published references will be further described in the statistical analysis plan to guide the analysis of MDS and AML response since the summary tables in the protocol do not provide all the details. **(Section 9.7)**

12. The Study Statistician for the study was changed from Dr. Mojtaba Noursalehi, PhD to Dr. Yong Hao, PhD.

All text changes that were made to the protocol for this amendment are shown in the redlined version.

APPENDIX 6: SUMMARY OF CHANGES, AMENDMENT 5

Protocol: SGI-110-01

Amendment Date: 18 February 2014

Amendment 5 allows treatment-naïve AML subjects who meet inclusion criteria to be treated with the 10-day treatment schedule in the Dose Expansion Segment.

Rationale for Amendment 5:

Based on emerging favorable efficacy and safety results from the Dose Expansion segment with the 10-day treatment regimen of SGI-110 in subjects with relapsed/refractory AML, the 10-day treatment schedule of SGI-110 in treatment-naïve subjects with AML will be investigated, as the study did not previously address this regimen in that subject population. Eligibility criteria for treatment-naïve elderly subjects were revised to include age ≥75 years because those subjects are usually not eligible for induction chemotherapy.

Summary of Changes:

A. Main Change:

1. Added text that treatment-naïve AML subjects will be allowed in the Dose Expansion Segment to receive open-label, 60 mg/m^2 SGI-110 dailyx10 in a single arm in at least 30 subjects and up to 50 subjects, similar to other study cohorts. **(Protocol Summary, Section 2.2, Section 4.1, Section 4.2.3, Section 5.1, Section 7.2, Section 9.0, and Section 11.1)**

2. Added age ≥75 years to the inclusion criteria necessary for an elderly AML subject to be eligible for the study. (**Section 5.2**)

B. Other minor or administrative changes for clarifications, corrections, or update to the study conduct:

1. CTA analysis is eliminated, and epigenetic markers are reduced to LINE-1 Course 1 and Day 1 of Course 2 only. **(Protocol Summary [Study Procedures and Assessments], Section 4.2.4, Section 9.0)**

2. Hematopoietic will be permitted if deemed medically necessary by the treating physician, not only in the case of a life-threatening septic event. (**Section 7.4.1.2**)

3. The Medical Monitor for the study was changed from Dr. Lynne Bui, MD to Dr. Mohammad Azab, MD.

APPENDIX 7: SUMMARY OF CHANGES, AMENDMENT 6

Protocol: SGI-110-01

Amendment Date: 09 May 2014

Amendment 6 provides for PK sampling and analysis of up to 20 treatment-naïve AML subjects treated in the Dose Expansion Segment. These subjects are currently being treated with the 10-day regimen.

Rationale for Amendment 6:

So far, PK has been evaluated only in subjects with relapsed/refractory AML who have received the 5-day regimen. In order to complete the study of SGI-110 PK profile in the different patient populations, this amendment is introduced to obtain PK sampling of up to 20 treatment-naïve AML subjects currently being treated with the 10-day regimen.

Summary of Changes:

1. The number of subjects for PK assessment in the Dose Expansion Segment of the study was revised to include up to 20 treatment-naïve subjects with AML who are treated with the 10-day regimen, with blood sampling on Course 1, Day 1 (pre-dose, 15 min, 30 min, 60 min, 90 min and 2 hr, 3 hr, 4 hr, 6 hr, and 8 hr post-dose) and sparse sampling on Course 1, Day 12 (pre-dose and 2 hr [±30 min] post-dose). **(Synopsis, Section 4.1, Section 9.0 [Table 2, Schedule of Events], and Section 9.2.1)**

Principal Investigators and Study Centres (Phase 2 Dose Expansion, Treatment-naïve patients)

Country	Principal Investigator (Center Number)	Study Center	Number (%) of TN AML Subjects[a] Enrolled (N=107)	Treated (N=103)
USA	Hagop Kantarjian, MD (replaced Jean-Pierre Issa, MD) (Center 3005)	The University of Texas MD Anderson Cancer Center Houston, TX	31 (29·0)	28 (27·2)
USA	Gail J Roboz, MD (Center 3001)	Weill Cornell Medical Center New York, NY	18 (16·8)	18 (17·5)
USA	Patricia Kropf, MD (Center 3036)	Temple BMT Program, Jeanes Hospital – Friends, Philadelphia, PA	13 (12·1)	13 (12·6)
Canada	Karen Yee, MD (Center 3027)	Princess Margaret Hospital Toronto, ON	9 (8·4)	9 (8·7)
USA	Casey O'Connell, MD (Center 3007)	USC/Norris Comprehensive Cancer Center, Los Angeles, CA	7 (6·5)	7 (6·8)
USA	Raoul Tibes, MD, PhD (Center 3008)	Mayo Clinic Scottsdale, AZ	6 (5·6)	6 (5·8)
USA	Katherine Walsh, MD (replaced William Blum, MD) (Center 3014)	The Ohio State University, James Cancer Hospital Columbus, OH	6 (5·6)	6 (5·9)
USA	Nikolai Podoltsev, MD (Center 3040)	Yale University School of Medicine New Haven, CT	5 (4·7)	5 (4·9)
USA	Elizabeth Griffiths, MD (Center 3026)	Roswell Park Cancer Institute Buffalo, NY	4 (3·7)	4 (3·9)
USA	David Rizzieri, MD (Center 3009)	Duke University Medical Center Durham, NC	2 (1·9)	2 (1·9)
USA	Wendy Stock, MD (Center 3032)	The University of Chicago Medicine Chicago, IL	2 (1·9)	2 (1·9)
USA	Scott Lunin, MD (replaced Thomas Ervin, MD) (Center 3037)	Florida Cancer Specialists – South Fort Myers, FL	2 (1·9)	1 (<1)
USA	Todd Rosenblat, MD (Center 3039)	Columbia University Medical Center New York, NY	1 (<1)	1 (<1)
USA	Jesus Berdeja, MD (replaced Michael Savona, MD) (Center 3035)	Sarah Cannon Research Institute Nashville, TN	1 (<1)	1 (<1)
		Total Enrolled	**107 (100)**	**103 (96·3)**

[a] Number of subjects enrolled is defined as the number randomized for subjects on the 5-day regimen and number who signed an informed consent for subjects on the 10-day regimen.

[b] One patient was enrolled at Dr. Lunin's centre, but transferred and was treated at Dr. Yee's centre.

Univariate and Multiple Cox Regression Analysis of Overall Survival

	Multiple Cox Regression Model				Univariate Cox Model	
Effect	**Hazard Ratio Estimate**	**95% Hazard Ratio Confidence Limits**		**p value**	**Hazard Ratio Estimate**	**p value**
ECOG (0-1 vs 2-3)	0·732	0·465	1·153	0·18	0·721	0·14
Cytogenetics (others vs poor)	0·853	0·547	1·331	0·48	0·836	0·42
Secondary AML (no vs yes)	1·015	0·628	1·641	0·95	1·228	0·36
Age (<75 vs ≥75 years)	1·360	0·803	2·301	0·25	1·155	0·57
Treatment (10-day vs 5-day)	1·037	0·662	1·625	0·87	1·083	0·72
PB blasts (<12% vs ≥12%)[a]	0·657	0·412	1·048	0·08	0·651	0·05

[a] 12% was the median value for baseline PB blast %

Supplement Table. Adverse events grade 3 or higher regardless of relationship to study treatment (≥5% of total)

	Number (%) of patients					
	5-Day			10-Day		
Adverse Event	**60 mg/m² (N=24)**	**90 mg/m² (N=27)**	**Total (N=51)**	**60 mg/m² (N=52)**	**Total (N=103)**
- Febrile neutropenia	15 (63)	16 (59)	31 (61)	36 (69)	67 (65)
- Thrombocytopenia	14 (58)	11 (41)	25 (49)	22 (42)	47 (46)
- Neutropenia	8 (33)	12 (44)	20 (39)	18 (35)	38 (37)
- Pneumonia	5 (21)	10 (37)	15 (29)	19 (37)	34 (33)
- Anaemia	8 (33)	7 (26)	15 (29)	12 (23)	27 (26)
- Sepsis	2 (8)	6 (22)	8 (16)	14 (27)	22 (21)
- Bacteraemia	3 (13)	3 (11)	6 (12)	8 (15)	14 (14)
- Hypokalaemia	2 (8)	5 (19)	7 (14)	6 (12)	13 (13)
- Leukopenia	5 (21)	6 (22)	11 (22)	2 (4)	13 (13)
- Cellulitis	2 (8)	3 (11)	5 (10)	5 (10)	10 (10)
- Hypotension	5 (21)	4 (15)	9 (18)	1 (2)	10 (10)
- Pyrexia	4 (17)	1 (4)	5 (10)	2 (4)	7 (7)
- Respiratory failure	1 (4)	1 (4)	2 (4)	5 (10)	7 (7)
- Syncope	4 (17)	2 (7)	6 (12)	1 (2)	7 (7)
- Fatigue	3 (13)	0	3 (6)	3 (6)	6 (6)
- Urinary tract infection	3 (13)	1 (4)	4 (8)	2 (4)	6 (6)
- Asthenia	0	1 (4)	1 (2)	4 (8)	5 (5)

Supplement Table. Adverse events (regardless of relationship to study treatment) by toxicity grade[a]

SYSTEM ORGAN CLASS:	5-Day Total (N=51)								10-Day Total (N=52)								Overall Total (N=103)							
- Preferred Term	G1-2		G3		G4		G5		G1-2		G3		G4		G5		G1-2		G3		G4		G5	
BLOOD AND LYMPHATIC SYSTEM DISORDERS:																								
- Anaemia	6	(12%)	14	(27%)	1	(2%)	0		2	(4%)	10	(19%)	2	(4%)	0		8	(8%)	24	(23%)	3	(3%)	0	
- Bone Marrow Failure	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Coagulopathy	1	(2%)	0		0		0		4	(8%)	0		0		0		5	(5%)	0		0		0	
- Disseminated Intravascular Coagulation	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Febrile Neutropenia	0		30	(59%)	0		1	(2%)	0		34	(65%)	2	(4%)	0		0		64	(62%)	2	(2%)	1	(<1%)
- Leukocytosis	0		0		0		0		2	(4%)	0		0		0		2	(2%)	0		0		0	
- Leukopenia	1	(2%)	3	(6%)	8	(16%)	0		0		0		2	(4%)	0		1	(<1%)	3	(3%)	10	(10%)	0	
- Lymphadenopathy	3	(6%)	0		0		0		1	(2%)	0		0		0		4	(4%)	0		0		0	
- Lymphatic Disorder	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Lymphopenia	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Neutropenia	1	(2%)	5	(10%)	15	(29%)	0		0		1	(2%)	17	(33%)	0		1	(<1%)	6	(6%)	32	(31%)	0	
- Pancytopenia	0		1	(2%)	1	(2%)	0		0		2	(4%)	0		0		0		3	(3%)	1	(<1%)	0	
- Thrombocytopenia	2	(4%)	5	(10%)	20	(39%)	0		3	(6%)	3	(6%)	19	(37%)	0		5	(5%)	8	(8%)	39	(38%)	0	
- Thrombocytosis	1	(2%)	0		0		0		1	(2%)	0		0		0		2	(2%)	0		0		0	
- Thrombotic Thrombocytopenic Purpura	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
CARDIAC DISORDERS:																								
- Acute Coronary Syndrome	0		0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0	
- Acute Myocardial Infarction	0		0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0	
- Angina Pectoris	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Arrhythmia	1	(2%)	0		0		0		2	(4%)	0		0		0		3	(3%)	0		0		0	
- Atrial Fibrillation	3	(6%)	2	(4%)	0		0		3	(6%)	1	(2%)	0		0		6	(6%)	3	(3%)	0		0	
- Cardiac Failure Congestive	1	(2%)	0		0		0		0		1	(2%)	0		0		1	(<1%)	1	(<1%)	0		0	
- Cardio-Respiratory Arrest	0		0		0		0		0		0		0		1	(2%)	0		0		0		1	(<1%)
- Cardiomyopathy	0		0		0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0	
- Left Ventricular Dysfunction	0		0		0		0		1	(2%)	1	(2%)	0		0		1	(<1%)	1	(<1%)	0		0	
- Myocardial Infarction	0		1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0	

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SYSTEM ORGAN CLASS:	5-Day Total (N=51)								10-Day Total (N=52)								Overall Total (N=103)							
- Preferred Term	**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**	
- Myocardial Ischaemia	0		0		0		1	(2%)	0		0		0		0		0		0		0		1	(<1%)
- Palpitations	1	(2%)	1	(2%)	0		0		2	(4%)	0		0		0		3	(3%)	1	(<1%)	0		0	
- Pericardial Effusion	0		0		0		1	(2%)	1	(2%)	0		0		0		1	(<1%)	0		0		1	(<1%)
- Pericarditis	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Sinus Tachycardia	1	(2%)	0		0		0		2	(4%)	0		0		0		3	(3%)	0		0		0	
- Tachycardia	1	(2%)	0		0		0		6	(12%)	0		0		0		7	(7%)	0		0		0	
- Ventricular Tachycardia	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
CONGENITAL, FAMILIAL AND GENETIC DISORDERS:																								
- Arteriovenous Malformation	0		0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0	
EAR AND LABYRINTH DISORDERS:																								
- Cerumen Impaction	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Ear Disorder	0		0		0		0		3	(6%)	0		0		0		3	(3%)	0		0		0	
- Ear Pain	0		0		0		0		2	(4%)	0		0		0		2	(2%)	0		0		0	
- Eustachian Tube Dysfunction	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Hearing Impaired	2	(4%)	0		0		0		0		0		0		0		2	(2%)	0		0		0	
- Vertigo	3	(6%)	0		0		0		0		0		0		0		3	(3%)	0		0		0	
ENDOCRINE DISORDERS:																								
- Adrenal Insufficiency	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Goitre	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Hypothyroidism	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
EYE DISORDERS:																								
- Blepharitis	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Conjunctival Haemorrhage	2	(4%)	0		0		0		1	(2%)	0		0		0		3	(3%)	0		0		0	
- Conjunctival Pallor	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Conjunctivitis	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Corneal Erosion	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Dry Eye	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Eye Irritation	1	(2%)	0		0		0		1	(2%)	0		0		0		2	(2%)	0		0		0	
- Eye Pain	2	(4%)	0		0		0		1	(2%)	0		0		0		3	(3%)	0		0		0	
- Eye Pruritus	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	

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SYSTEM ORGAN CLASS:	5-Day Total (N=51)								10-Day Total (N=52)								Overall Total (N=103)							
- Preferred Term	**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**	
- Eye Swelling	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Eyelid Disorder	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Keratitis	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Ocular Hyperaemia	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Periorbital Oedema	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Photophobia	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Pupillary Disorder	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Scleral Pigmentation	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Vision Blurred	2	(4%)	0		0		0		2	(4%)	0		0		0		4	(4%)	0		0		0	
GASTROINTESTINAL DISORDERS:																								
- Abdominal Discomfort	1	(2%)	0		0		0		3	(6%)	0		0		0		4	(4%)	0		0		0	
- Abdominal Distension	4	(8%)	0		0		0		5	(10%)	0		0		0		9	(9%)	0		0		0	
- Abdominal Pain	11	(22%)	0		0		0		4	(8%)	2	(4%)	0		0		15	(15%)	2	(2%)	0		0	
- Abdominal Pain Upper	2	(4%)	0		0		0		3	(6%)	0		0		0		5	(5%)	0		0		0	
- Anal Fissure	0		1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0	
- Cheilitis	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Colitis	0		0		0		0		0		4	(8%)	0		0		0		4	(4%)	0		0	
- Constipation	25	(49%)	1	(2%)	0		0		31	(60%)	2	(4%)	0		0		56	(54%)	3	(3%)	0		0	
- Dental Caries	1	(2%)	0		0		0		1	(2%)	0		0		0		2	(2%)	0		0		0	
- Dental Discomfort	0		0		0		0		2	(4%)	0		0		0		2	(2%)	0		0		0	
- Diarrhoea	22	(43%)	0		0		0		29	(56%)	2	(4%)	0		0		51	(50%)	2	(2%)	0		0	
- Diverticulum	1	(2%)	0		0		0		1	(2%)	0		0		0		2	(2%)	0		0		0	
- Dry Mouth	3	(6%)	0		0		0		7	(13%)	0		0		0		10	(10%)	0		0		0	
- Duodenal Ulcer Haemorrhage	0		1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0	
- Dyspepsia	4	(8%)	0		0		0		5	(10%)	0		0		0		9	(9%)	0		0		0	
- Dysphagia	4	(8%)	0		0		0		3	(6%)	0		0		0		7	(7%)	0		0		0	
- Enteritis	0		0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0	
- Enterocolitis	0		0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0	
- Epigastric Discomfort	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Eructation	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Faecal Incontinence	2	(4%)	0		0		0		1	(2%)	0		0		0		3	(3%)	0		0		0	
- Faeces Discoloured	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Flatulence	1	(2%)	0		0		0		1	(2%)	0		0		0		2	(2%)	0		0		0	
- Gastritis	0		0		0		0		1	(2%)	1	(2%)	0		0		1	(<1%)	1	(<1%)	0		0	

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SYSTEM ORGAN CLASS:	5-Day Total (N=51)								10-Day Total (N=52)								Overall Total (N=103)							
- Preferred Term	**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**	
- Gastrointestinal Haemorrhage	0		1	(2%)	0		0		0		2	(4%)	0		0		0		3	(3%)	0		0	
- Gastrointestinal Pain	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Gastrooesophageal Reflux Disease	5	(10%)	0		0		0		2	(4%)	0		0		0		7	(7%)	0		0		0	
- Gingival Bleeding	3	(6%)	0		0		0		1	(2%)	0		0		0		4	(4%)	0		0		0	
- Gingival Hypertrophy	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Gingival Pain	2	(4%)	0		0		0		1	(2%)	0		0		0		3	(3%)	0		0		0	
- Glossodynia	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Haematochezia	0		1	(2%)	0		0		1	(2%)	0		0		0		1	(<1%)	1	(<1%)	0		0	
- Haemorrhoids	4	(8%)	0		0		0		5	(10%)	0		0		0		9	(9%)	0		0		0	
- Hypoaesthesia Oral	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Ileus	0		1	(2%)	0		0		1	(2%)	1	(2%)	0		0		1	(<1%)	2	(2%)	0		0	
- Lip Blister	1	(2%)	0		0		0		3	(6%)	0		0		0		4	(4%)	0		0		0	
- Lip Pain	0		0		0		0		2	(4%)	0		0		0		2	(2%)	0		0		0	
- Lip Ulceration	0		0		0		0		2	(4%)	0		0		0		2	(2%)	0		0		0	
- Loose Tooth	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Lower Gastrointestinal Haemorrhage	0		1	(2%)	0		0		0		1	(2%)	0		0		0		2	(2%)	0		0	
- Melaena	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Mouth Haemorrhage	3	(6%)	1	(2%)	0		0		3	(6%)	0		0		0		6	(6%)	1	(<1%)	0		0	
- Mouth Ulceration	1	(2%)	0		0		0		2	(4%)	0		0		0		3	(3%)	0		0		0	
- Nausea	22	(43%)	2	(4%)	0		0		25	(48%)	1	(2%)	0		0		47	(46%)	3	(3%)	0		0	
- Oesophageal Ulcer	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Oral Disorder	1	(2%)	0		0		0		2	(4%)	0		0		0		3	(3%)	0		0		0	
- Oral Pain	4	(8%)	0		0		0		2	(4%)	0		0		0		6	(6%)	0		0		0	
- Pancreatitis	1	(2%)	1	(2%)	0		0		0		0		0		0		1	(<1%)	1	(<1%)	0		0	
- Paraesthesia Oral	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Periodontal Disease	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Rectal Haemorrhage	2	(4%)	1	(2%)	0		0		1	(2%)	0		0		0		3	(3%)	1	(<1%)	0		0	
- Regurgitation	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Salivary Hypersecretion	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Small Intestinal Obstruction	0		1	(2%)	0		0		0		2	(4%)	0		0		0		3	(3%)	0		0	
- Stomatitis	13	(25%)	0		0		0		14	(27%)	1	(2%)	0		0		27	(26%)	1	(<1%)	0		0	
- Tongue Ulceration	2	(4%)	0		0		0		0		0		0		0		2	(2%)	0		0		0	
- Tooth Disorder	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Toothache	2	(4%)	0		0		0		2	(4%)	0		0		0		4	(4%)	0		0		0	
- Upper Gastrointestinal Haemorrhage	0		0		0		0		0		2	(4%)	0		0		0		2	(2%)	0		0	

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SYSTEM ORGAN CLASS:	5-Day Total (N=51)								10-Day Total (N=52)								Overall Total (N=103)							
- Preferred Term	**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**	
- Vomiting	9	(18%)	2	(4%)	0		0		16	(31%)	0		0		0		25	(24%)	2	(2%)	0		0	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS:																								
- Adverse Drug Reaction	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Application Site Bleeding	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Asthenia	11	(22%)	1	(2%)	0		0		15	(29%)	4	(8%)	0		0		26	(25%)	5	(5%)	0		0	
- Catheter Site Erythema	1	(2%)	0		0		0		1	(2%)	0		0		0		2	(2%)	0		0		0	
- Catheter Site Haemorrhage	1	(2%)	0		0		0		1	(2%)	0		0		0		2	(2%)	0		0		0	
- Catheter Site Pain	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Chest Discomfort	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Chest Pain	3	(6%)	0		0		0		2	(4%)	3	(6%)	0		0		5	(5%)	3	(3%)	0		0	
- Chills	5	(10%)	0		0		0		6	(12%)	0		0		0		11	(11%)	0		0		0	
- Device Occlusion	2	(4%)	0		0		0		0		0		0		0		2	(2%)	0		0		0	
- Fatigue	18	(35%)	3	(6%)	0		0		23	(44%)	3	(6%)	0		0		41	(40%)	6	(6%)	0		0	
- Gait Disturbance	1	(2%)	0		0		0		2	(4%)	0		0		0		3	(3%)	0		0		0	
- Generalised Oedema	0		0		0		0		2	(4%)	0		0		0		2	(2%)	0		0		0	
- Infusion Site Reaction	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Injection Site Discomfort	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Injection Site Erythema	2	(4%)	0		0		0		0		0		0		0		2	(2%)	0		0		0	
- Injection Site Haematoma	8	(16%)	0		0		0		1	(2%)	0		0		0		9	(9%)	0		0		0	
- Injection Site Haemorrhage	8	(16%)	0		0		0		0		0		0		0		8	(8%)	0		0		0	
- Injection Site Inflammation	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Injection Site Joint Redness	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Injection Site Nodule	7	(14%)	0		0		0		6	(12%)	0		0		0		13	(13%)	0		0		0	
- Injection Site Pain	27	(53%)	0		0		0		6	(12%)	0		0		0		33	(32%)	0		0		0	
- Injection Site Reaction	4	(8%)	1	(2%)	0		0		7	(13%)	0		0		0		11	(11%)	1	(<1%)	0		0	
- Localised Oedema	3	(6%)	0		0		0		0		0		0		0		3	(3%)	0		0		0	
- Malaise	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Mass	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Mucosal Dryness	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Multi-Organ Failure	0		0		0		1	(2%)	0		0		0		1	(2%)	0		0		0		2	(2%)
- Nodule	1	(2%)	0		0		0		1	(2%)	0		0		0		2	(2%)	0		0		0	
- Non-Cardiac Chest Pain	2	(4%)	1	(2%)	0		0		3	(6%)	0		0		0		5	(5%)	1	(<1%)	0		0	
- Oedema	4	(8%)	0		0		0		11	(21%)	1	(2%)	0		0		15	(15%)	1	(<1%)	0		0	

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SYSTEM ORGAN CLASS:	5-Day Total (N=51)								10-Day Total (N=52)								Overall Total (N=103)							
- Preferred Term	**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**	
- Oedema Peripheral	18	(35%)	0		0		0		14	(27%)	1	(2%)	0		0		32	(31%)	1	(<1%)	0		0	
- Pain	7	(14%)	0		0		0		13	(25%)	0		0		0		20	(19%)	0		0		0	
- Pyrexia	10	(20%)	5	(10%)	0		0		9	(17%)	2	(4%)	0		0		19	(18%)	7	(7%)	0		0	
- Swelling	0		0		0		0		2	(4%)	0		0		0		2	(2%)	0		0		0	
- Ulcer	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Vessel Puncture Site Pain	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
HEPATOBILIARY DISORDERS:																								
- Any Event	0		0		0		0		1	(2%)	2	(4%)	0		0		1	(<1%)	2	(2%)	0		0	
- Cholecystitis	0		0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0	
- Cholecystitis Acute	0		0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0	
- Hyperbilirubinaemia	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
IMMUNE SYSTEM DISORDERS:																								
- Drug Hypersensitivity	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Hypersensitivity	2	(4%)	0		0		0		1	(2%)	0		0		0		3	(3%)	0		0		0	
- Sarcoidosis	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Seasonal Allergy	0		0		0		0		2	(4%)	0		0		0		2	(2%)	0		0		0	
INFECTIONS AND INFESTATIONS:																								
- Abdominal Wall Abscess	0		1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0	
- Abscess	0		1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0	
- Bacteraemia	0		5	(10%)	1	(2%)	0		0		7	(13%)	1	(2%)	0		0		12	(12%)	2	(2%)	0	
- Candidiasis	2	(4%)	0		0		0		4	(8%)	0		0		0		6	(6%)	0		0		0	
- Cellulitis	3	(6%)	5	(10%)	0		0		10	(19%)	5	(10%)	0		0		13	(13%)	10	(10%)	0		0	
- Cellulitis Orbital	0		0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0	
- Chronic Sinusitis	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Clostridium Difficile Colitis	1	(2%)	0		0		0		1	(2%)	0		0		0		2	(2%)	0		0		0	
- Corona Virus Infection	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Cystitis	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Device Related Infection	0		0		0		0		1	(2%)	1	(2%)	0		0		1	(<1%)	1	(<1%)	0		0	
- Diarrhoea Infectious	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Diverticulitis	0		2	(4%)	0		0		0		1	(2%)	0		0		0		3	(3%)	0		0	
- Epiglottitis	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Escherichia Bacteraemia	0		0		1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0	

[a] Only the highest grade is included for patients who experienced a particular event more than once.

SYSTEM ORGAN CLASS:	5-Day Total (N=51)								10-Day Total (N=52)								Overall Total (N=103)							
- Preferred Term	**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**	
- Escherichia Infection	0		0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0	
- External Ear Cellulitis	0		1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0	
- Folliculitis	3	(6%)	0		0		0		0		0		0		0		3	(3%)	0		0		0	
- Gastroenteritis	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Genital Abscess	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Herpes Simplex	3	(6%)	0		0		0		1	(2%)	0		0		0		4	(4%)	0		0		0	
- Herpes Virus Infection	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Infection	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Influenza	0		1	(2%)	0		0		0		1	(2%)	0		0		0		2	(2%)	0		0	
- Injection Site Infection	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Mycobacterium Avium Complex Infection	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Oral Candidiasis	1	(2%)	0		0		0		3	(6%)	0		0		0		4	(4%)	0		0		0	
- Oral Infection	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Otitis Media	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Paronychia	1	(2%)	0		0		0		1	(2%)	0		0		0		2	(2%)	0		0		0	
- Periorbital Cellulitis	0		0		0		0		0		2	(4%)	0		0		0		2	(2%)	0		0	
- Periorbital Infection	0		0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0	
- Peritonsillar Abscess	0		1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0	
- Pharyngeal Abscess	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Pharyngitis	0		2	(4%)	0		0		0		0		0		0		0		2	(2%)	0		0	
- Pharyngitis Streptococcal	0		2	(4%)	0		0		0		0		0		0		0		2	(2%)	0		0	
- Pneumonia	4	(8%)	12	(24%)	1	(2%)	2	(4%)	1	(2%)	16	(31%)	0		3	(6%)	5	(5%)	28	(27%)	1	(<1%)	5	(5%)
- Pneumonia Bacterial	0		1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0	
- Rectal Abscess	0		1	(2%)	0		0		1	(2%)	0		0		0		1	(<1%)	1	(<1%)	0		0	
- Rhinitis	1	(2%)	0		0		0		1	(2%)	0		0		0		2	(2%)	0		0		0	
- Sepsis	0		4	(8%)	2	(4%)	2	(4%)	0		5	(10%)	3	(6%)	6	(12%)	0		9	(9%)	5	(5%)	8	(8%)
- Sinusitis	1	(2%)	0		0		0		3	(6%)	2	(4%)	0		0		4	(4%)	2	(2%)	0		0	
- Staphylococcal Infection	0		0		0		0		0		3	(6%)	0		0		0		3	(3%)	0		0	
- Tooth Infection	0		1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0	
- Upper Respiratory Fungal Infection	0		0		0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0	
- Upper Respiratory Tract Infection	4	(8%)	2	(4%)	0		0		4	(8%)	0		0		0		8	(8%)	2	(2%)	0		0	
- Urinary Tract Infection	2	(4%)	4	(8%)	0		0		5	(10%)	2	(4%)	0		0		7	(7%)	6	(6%)	0		0	
- Viral Infection	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Viral Pharyngitis	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Wound Infection	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	

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SYSTEM ORGAN CLASS:	5-Day Total (N=51)								10-Day Total (N=52)								Overall Total (N=103)							
- Preferred Term	**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS:																								
- Allergic Transfusion Reaction	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Arthropod Bite	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Contusion	13	(25%)	0		0		0		11	(21%)	0		0		0		24	(23%)	0		0		0	
- Excoriation	4	(8%)	0		0		0		1	(2%)	0		0		0		5	(5%)	0		0		0	
- Facial Bones Fracture	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Fall	4	(8%)	0		0		0		9	(17%)	1	(2%)	0		0		13	(13%)	1	(<1%)	0		0	
- Hip Fracture	0		1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0	
- Infusion Related Reaction	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Jaw Fracture	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Laceration	0		0		0		0		2	(4%)	0		0		0		2	(2%)	0		0		0	
- Limb Injury	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Penis Injury	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Periorbital Haematoma	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Rib Fracture	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Subdural Haematoma	2	(4%)	2	(4%)	1	(2%)	0		0		0		0		0		2	(2%)	2	(2%)	1	(<1%)	0	
- Sunburn	1	(2%)	0		0		0		2	(4%)	0		0		0		3	(3%)	0		0		0	
- Tendon Rupture	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Thermal Burn	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Transfusion Reaction	3	(6%)	2	(4%)	0		0		5	(10%)	0		0		0		8	(8%)	2	(2%)	0		0	
- Transfusion-Related Circulatory Overload	0		1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0	
- Wound	1	(2%)	0		0		0		1	(2%)	0		0		0		2	(2%)	0		0		0	
INVESTIGATIONS:																								
- Alanine Aminotransferase Increased	2	(4%)	0		0		0		6	(12%)	0		0		0		8	(8%)	0		0		0	
- Aspartate Aminotransferase Increased	2	(4%)	0		0		0		3	(6%)	0		0		0		5	(5%)	0		0		0	
- Aspergillus Test Positive	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Blood Alkaline Phosphatase Increased	0		1	(2%)	0		0		1	(2%)	0		0		0		1	(<1%)	1	(<1%)	0		0	
- Blood Bilirubin Increased	2	(4%)	1	(2%)	0		0		2	(4%)	0		0		0		4	(4%)	1	(<1%)	0		0	
- Blood Creatine Increased	1	(2%)	0		0		0		2	(4%)	0		0		0		3	(3%)	0		0		0	
- Blood Creatinine Increased	4	(8%)	0		0		0		4	(8%)	0		0		0		8	(8%)	0		0		0	
- Blood Phosphorus Decreased	0		0		0		0		1	(2%)	1	(2%)	0		0		1	(<1%)	1	(<1%)	0		0	
- Blood Urea Increased	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	

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SYSTEM ORGAN CLASS:	5-Day Total (N=51)								10-Day Total (N=52)								Overall Total (N=103)							
- Preferred Term	**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**	
- Blood Uric Acid Increased	1	(2%)	1	(2%)	0		0		0		0		0		0		1	(<1%)	1	(<1%)	0		0	
- Cardiac Murmur	0		0		0		0		2	(4%)	0		0		0		2	(2%)	0		0		0	
- Electrocardiogram Qt Prolonged	1	(2%)	0		0		0		0		1	(2%)	0		0		1	(<1%)	1	(<1%)	0		0	
- Enterobacter Test Positive	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Gamma-Glutamyltransferase Increased	0		0		1	(2%)	0		1	(2%)	0		0		0		1	(<1%)	0		1	(<1%)	0	
- Haemoglobin Decreased	0		0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0	
- International Normalised Ratio Increased	1	(2%)	0		0		0		2	(4%)	0		0		0		3	(3%)	0		0		0	
- Liver Function Test Abnormal	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Platelet Count Decreased	0		0		0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0	
- Transaminases Increased	0		0		0		0		2	(4%)	0		0		0		2	(2%)	0		0		0	
- Weight Decreased	6	(12%)	0		0		0		2	(4%)	1	(2%)	0		0		8	(8%)	1	(<1%)	0		0	
- Weight Increased	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- White Blood Cell Count Increased	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
METABOLISM AND NUTRITION DISORDERS:																								
- Acidosis	0		1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0	
- Alkalosis Hypochloraemic	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Cachexia	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Decreased Appetite	22	(43%)	0		0		0		20	(38%)	0		0		0		42	(41%)	0		0		0	
- Dehydration	3	(6%)	0		0		0		3	(6%)	0		0		0		6	(6%)	0		0		0	
- Diabetes Mellitus	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Electrolyte Imbalance	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Failure To Thrive	1	(2%)	1	(2%)	0		0		1	(2%)	0		0		0		2	(2%)	1	(<1%)	0		0	
- Fluid Overload	4	(8%)	0		0		0		10	(19%)	0		0		0		14	(14%)	0		0		0	
- Fluid Retention	0		0		0		0		2	(4%)	0		0		0		2	(2%)	0		0		0	
- Gout	0		0		0		0		2	(4%)	0		0		0		2	(2%)	0		0		0	
- Hypercalcaemia	3	(6%)	0		0		0		0		0		0		0		3	(3%)	0		0		0	
- Hyperglycaemia	4	(8%)	2	(4%)	0		0		3	(6%)	0		0		0		7	(7%)	2	(2%)	0		0	
- Hyperkalaemia	2	(4%)	0		0		0		1	(2%)	0		0		0		3	(3%)	0		0		0	
- Hypermagnesaemia	0		1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0	
- Hypernatraemia	0		1	(2%)	0		0		1	(2%)	0		0		0		1	(<1%)	1	(<1%)	0		0	
- Hyperphosphataemia	3	(6%)	0		0		0		1	(2%)	2	(4%)	0		0		4	(4%)	2	(2%)	0		0	
- Hyperuricaemia	3	(6%)	1	(2%)	1	(2%)	0		3	(6%)	0		0		0		6	(6%)	1	(<1%)	1	(<1%)	0	
- Hypervolaemia	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	

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SYSTEM ORGAN CLASS:	5-Day Total (N=51)								10-Day Total (N=52)								Overall Total (N=103)							
- Preferred Term	**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**	
- Hypoalbuminaemia	2	(4%)	0		0		0		3	(6%)	0		0		0		5	(5%)	0		0		0	
- Hypocalcaemia	4	(8%)	2	(4%)	0		0		3	(6%)	1	(2%)	0		0		7	(7%)	3	(3%)	0		0	
- Hypoglycaemia	0		2	(4%)	0		0		0		1	(2%)	0		0		0		3	(3%)	0		0	
- Hypokalaemia	16	(31%)	7	(14%)	0		0		21	(40%)	6	(12%)	0		0		37	(36%)	13	(13%)	0		0	
- Hypomagnesaemia	14	(27%)	0		0		0		23	(44%)	0		0		0		37	(36%)	0		0		0	
- Hyponatraemia	6	(12%)	0		0		0		5	(10%)	3	(6%)	0		0		11	(11%)	3	(3%)	0		0	
- Hypophosphataemia	6	(12%)	2	(4%)	0		0		4	(8%)	2	(4%)	0		0		10	(10%)	4	(4%)	0		0	
- Hypouricaemia	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Metabolic Acidosis	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Metabolic Alkalosis	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Tumour Lysis Syndrome	0		1	(2%)	0		0		1	(2%)	0		0		0		1	(<1%)	1	(<1%)	0		0	
- Vitamin D Deficiency	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS:																								
- Arthralgia	7	(14%)	1	(2%)	0		0		7	(13%)	1	(2%)	0		0		14	(14%)	2	(2%)	0		0	
- Arthritis	0		0		0		0		2	(4%)	0		0		0		2	(2%)	0		0		0	
- Back Pain	8	(16%)	1	(2%)	0		0		12	(23%)	0		0		0		20	(19%)	1	(<1%)	0		0	
- Bone Pain	1	(2%)	0		0		0		2	(4%)	0		0		0		3	(3%)	0		0		0	
- Bursitis	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Flank Pain	2	(4%)	0		0		0		0		0		0		0		2	(2%)	0		0		0	
- Groin Pain	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Joint Swelling	2	(4%)	0		0		0		0		0		0		0		2	(2%)	0		0		0	
- Mobility Decreased	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Muscle Atrophy	0		0		0		0		2	(4%)	0		0		0		2	(2%)	0		0		0	
- Muscle Spasms	2	(4%)	0		0		0		3	(6%)	0		0		0		5	(5%)	0		0		0	
- Muscular Weakness	3	(6%)	3	(6%)	0		0		3	(6%)	0		0		0		6	(6%)	3	(3%)	0		0	
- Musculoskeletal Chest Pain	0		0		0		0		3	(6%)	0		0		0		3	(3%)	0		0		0	
- Musculoskeletal Pain	4	(8%)	0		0		0		3	(6%)	0		0		0		7	(7%)	0		0		0	
- Musculoskeletal Stiffness	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Myalgia	2	(4%)	1	(2%)	0		0		4	(8%)	0		0		0		6	(6%)	1	(<1%)	0		0	
- Neck Pain	1	(2%)	0		0		0		1	(2%)	0		0		0		2	(2%)	0		0		0	
- Pain In Extremity	5	(10%)	0		0		0		7	(13%)	0		0		0		12	(12%)	0		0		0	
- Pain In Jaw	0		0		0		0		2	(4%)	0		0		0		2	(2%)	0		0		0	
- Rotator Cuff Syndrome	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	

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SYSTEM ORGAN CLASS:	5-Day Total (N=51)								10-Day Total (N=52)								Overall Total (N=103)							
- Preferred Term	**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**	
- Synovial Cyst	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Temporomandibular Joint Syndrome	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS):																								
- Lip Neoplasm Malignant Stage Unspecified	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Lung Adenocarcinoma Metastatic	0		0		0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0	
- Squamous Cell Carcinoma	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
NERVOUS SYSTEM DISORDERS:																								
- Amnesia	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Balance Disorder	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Cerebral Infarction	0		1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0	
- Diabetic Neuropathy	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Disturbance In Attention	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Dizziness	14	(27%)	0		0		0		14	(27%)	0		0		0		28	(27%)	0		0		0	
- Dysgeusia	6	(12%)	0		0		0		3	(6%)	0		0		0		9	(9%)	0		0		0	
- Haemorrhage Intracranial	0		0		0		1	(2%)	0		0		0		1	(2%)	0		0		0		2	(2%)
- Headache	11	(22%)	1	(2%)	0		0		8	(15%)	0		0		0		19	(18%)	1	(<1%)	0		0	
- Lethargy	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Muscle Contractions Involuntary	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Neuralgia	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Neurological Decompensation	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Neuropathy Peripheral	0		0		0		0		3	(6%)	0		0		0		3	(3%)	0		0		0	
- Paraesthesia	2	(4%)	0		0		0		1	(2%)	0		0		0		3	(3%)	0		0		0	
- Presyncope	1	(2%)	1	(2%)	0		0		0		0		0		0		1	(<1%)	1	(<1%)	0		0	
- Sciatica	0		1	(2%)	0		0		1	(2%)	0		0		0		1	(<1%)	1	(<1%)	0		0	
- Sedation	0		1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0	
- Somnolence	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Syncope	1	(2%)	6	(12%)	0		0		2	(4%)	1	(2%)	0		0		3	(3%)	7	(7%)	0		0	
- Tremor	1	(2%)	0		0		0		3	(6%)	0		0		0		4	(4%)	0		0		0	
- Tunnel Vision	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
PSYCHIATRIC DISORDERS:																								

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SYSTEM ORGAN CLASS:	5-Day Total (N=51)								10-Day Total (N=52)								Overall Total (N=103)							
- Preferred Term	**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**	
- Agitation	2	(4%)	1	(2%)	0		0		0		0		0		0		2	(2%)	1	(<1%)	0		0	
- Anxiety	3	(6%)	0		0		0		14	(27%)	0		0		0		17	(17%)	0		0		0	
- Confusional State	5	(10%)	4	(8%)	0		0		10	(19%)	0		0		0		15	(15%)	4	(4%)	0		0	
- Delirium	1	(2%)	1	(2%)	0		0		3	(6%)	0		0		0		4	(4%)	1	(<1%)	0		0	
- Delirium Febrile	0		0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0	
- Depression	8	(16%)	0		0		0		5	(10%)	0		0		0		13	(13%)	0		0		0	
- Hallucination	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Hallucination, Visual	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Insomnia	11	(22%)	0		0		0		6	(12%)	0		0		0		17	(17%)	0		0		0	
- Psychotic Disorder	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Restlessness	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
RENAL AND URINARY DISORDERS:																								
- Bladder Pain	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Bladder Spasm	1	(2%)	0		0		0		3	(6%)	0		0		0		4	(4%)	0		0		0	
- Dysuria	3	(6%)	0		0		0		1	(2%)	0		0		0		4	(4%)	0		0		0	
- Haematuria	0		0		0		0		5	(10%)	2	(4%)	0		0		5	(5%)	2	(2%)	0		0	
- Nephrolithiasis	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Nocturia	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Polyuria	4	(8%)	0		0		0		2	(4%)	0		0		0		6	(6%)	0		0		0	
- Proteinuria	0		2	(4%)	0		0		0		0		0		0		0		2	(2%)	0		0	
- Renal Failure	2	(4%)	1	(2%)	0		0		2	(4%)	1	(2%)	0		0		4	(4%)	2	(2%)	0		0	
- Renal Failure Acute	1	(2%)	1	(2%)	0		0		3	(6%)	0		0		0		4	(4%)	1	(<1%)	0		0	
- Renal Failure Chronic	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Urinary Hesitation	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Urinary Incontinence	2	(4%)	0		0		0		1	(2%)	0		0		0		3	(3%)	0		0		0	
- Urinary Retention	0		0		0		0		6	(12%)	2	(4%)	0		0		6	(6%)	2	(2%)	0		0	
- Urine Odour Abnormal	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS:																								
- Breast Discomfort	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Testicular Pain	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Vaginal Discharge	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Vaginal Haemorrhage	0		0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0	

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SYSTEM ORGAN CLASS:	5-Day Total (N=51)								10-Day Total (N=52)								Overall Total (N=103)							
- Preferred Term	**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS:																								
- Acute Respiratory Failure	0		0		1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0	
- Atelectasis	1	(2%)	0		0		0		1	(2%)	1	(2%)	0		0		2	(2%)	1	(<1%)	0		0	
- Bronchospasm	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Chronic Obstructive Pulmonary Disease	0		0		0		0		2	(4%)	0		0		0		2	(2%)	0		0		0	
- Cough	15	(29%)	0		0		0		20	(38%)	0		0		0		35	(34%)	0		0		0	
- Dry Throat	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Dysphonia	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Dyspnoea	19	(37%)	0		0		0		24	(46%)	2	(4%)	0		0		43	(42%)	2	(2%)	0		0	
- Dyspnoea Exertional	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Epistaxis	10	(20%)	0		0		0		13	(25%)	2	(4%)	0		0		23	(22%)	2	(2%)	0		0	
- Haemoptysis	1	(2%)	0		0		0		2	(4%)	0		0		0		3	(3%)	0		0		0	
- Hypoxia	0		2	(4%)	0		0		2	(4%)	1	(2%)	0		0		2	(2%)	3	(3%)	0		0	
- Increased Upper Airway Secretion	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Nasal Congestion	0		0		0		0		3	(6%)	0		0		0		3	(3%)	0		0		0	
- Nasal Discomfort	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Nasal Dryness	2	(4%)	0		0		0		0		0		0		0		2	(2%)	0		0		0	
- Nasal Necrosis	0		0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0	
- Oropharyngeal Pain	7	(14%)	0		0		0		13	(25%)	0		0		0		20	(19%)	0		0		0	
- Oropharyngeal Swelling	0		0		1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0	
- Pharyngeal Disorder	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Pleural Effusion	3	(6%)	0		0		0		9	(17%)	0		0		0		12	(12%)	0		0		0	
- Pleuritic Pain	0		1	(2%)	0		0		0		1	(2%)	0		0		0		2	(2%)	0		0	
- Pneumonitis	0		0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0	
- Productive Cough	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Pulmonary Embolism	0		0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0	
- Pulmonary Oedema	1	(2%)	0		0		0		0		1	(2%)	0		0		1	(<1%)	1	(<1%)	0		0	
- Respiratory Failure	0		1	(2%)	1	(2%)	0		0		0		3	(6%)	2	(4%)	0		1	(<1%)	4	(4%)	2	(2%)
- Rhinitis Allergic	1	(2%)	0		0		0		1	(2%)	0		0		0		2	(2%)	0		0		0	
- Rhinorrhoea	3	(6%)	0		0		0		7	(13%)	0		0		0		10	(10%)	0		0		0	
- Sleep Apnoea Syndrome	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Tachypnoea	0		0		0		0		1	(2%)	1	(2%)	0		0		1	(<1%)	1	(<1%)	0		0	
- Throat Irritation	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	

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SYSTEM ORGAN CLASS:	5-Day Total (N=51)								10-Day Total (N=52)								Overall Total (N=103)							
- Preferred Term	**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**	
- Upper-Airway Cough Syndrome	1	(2%)	0		0		0		1	(2%)	1	(2%)	0		0		2	(2%)	1	(<1%)	0		0	
- Wheezing	1	(2%)	0		0		0		2	(4%)	0		0		0		3	(3%)	0		0		0	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS:																								
- Acne	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Actinic Keratosis	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Acute Febrile Neutrophilic Dermatosis	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Alopecia	3	(6%)	0		0		0		1	(2%)	0		0		0		4	(4%)	0		0		0	
- Blister	1	(2%)	0		0		0		2	(4%)	0		0		0		3	(3%)	0		0		0	
- Butterfly Rash	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Cold Sweat	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Decubitus Ulcer	1	(2%)	0		0		0		4	(8%)	0		0		0		5	(5%)	0		0		0	
- Dermatitis	0		0		0		0		2	(4%)	0		0		0		2	(2%)	0		0		0	
- Dry Skin	2	(4%)	0		0		0		5	(10%)	0		0		0		7	(7%)	0		0		0	
- Ecchymosis	3	(6%)	0		0		0		11	(21%)	0		0		0		14	(14%)	0		0		0	
- Erythema	4	(8%)	1	(2%)	0		0		9	(17%)	0		0		0		13	(13%)	1	(<1%)	0		0	
- Erythema Multiforme	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Hyperhidrosis	1	(2%)	0		0		0		4	(8%)	0		0		0		5	(5%)	0		0		0	
- Hypoaesthesia Facial	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Ingrowing Nail	1	(2%)	0		0		0		2	(4%)	0		0		0		3	(3%)	0		0		0	
- Lipohypertrophy	4	(8%)	0		0		0		0		0		0		0		4	(4%)	0		0		0	
- Night Sweats	1	(2%)	0		0		0		8	(15%)	0		0		0		9	(9%)	0		0		0	
- Onychoclasis	1	(2%)	0		0		0		1	(2%)	0		0		0		2	(2%)	0		0		0	
- Onychomadesis	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Palmar-Plantar Erythrodysaesthesia Syndrome	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Petechiae	7	(14%)	0		0		0		5	(10%)	0		0		0		12	(12%)	0		0		0	
- Pruritus	3	(6%)	0		0		0		6	(12%)	0		0		0		9	(9%)	0		0		0	
- Rash	5	(10%)	0		0		0		11	(21%)	0		0		0		16	(16%)	0		0		0	
- Rash Erythematous	3	(6%)	0		0		0		2	(4%)	0		0		0		5	(5%)	0		0		0	
- Rash Maculo-Papular	2	(4%)	0		0		0		0		0		0		0		2	(2%)	0		0		0	
- Rash Morbilliform	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Seborrhoea	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Seborrhoeic Dermatitis	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	

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SYSTEM ORGAN CLASS:	5-Day Total (N=51)								10-Day Total (N=52)								Overall Total (N=103)							
- Preferred Term	**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**		**G1-2**		**G3**		**G4**		**G5**	
- Skin Hyperpigmentation	1	(2%)	0		0		0		1	(2%)	0		0		0		2	(2%)	0		0		0	
- Skin Irritation	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Skin Lesion	4	(8%)	0		0		0		5	(10%)	0		0		0		9	(9%)	0		0		0	
- Skin Ulcer	0		1	(2%)	0		0		1	(2%)	0		0		0		1	(<1%)	1	(<1%)	0		0	
- Swelling Face	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Toxic Skin Eruption	0		0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0	
- Urticaria	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
SURGICAL AND MEDICAL PROCEDURES:																								
- Nail Operation	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Sinus Operation	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Tooth Extraction	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Vagotomy	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
VASCULAR DISORDERS:																								
- Deep Vein Thrombosis	2	(4%)	1	(2%)	0		0		4	(8%)	1	(2%)	0		0		6	(6%)	2	(2%)	0		0	
- Haematoma	5	(10%)	1	(2%)	0		0		2	(4%)	0		0		0		7	(7%)	1	(<1%)	0		0	
- Haemorrhage	1	(2%)	0		0		0		2	(4%)	0		0		0		3	(3%)	0		0		0	
- Hypertension	1	(2%)	2	(4%)	0		0		0		0		0		0		1	(<1%)	2	(2%)	0		0	
- Hypoperfusion	0		0		0		0		1	(2%)	0		0		0		1	(<1%)	0		0		0	
- Hypotension	1	(2%)	9	(18%)	0		0		9	(17%)	1	(2%)	0		0		10	(10%)	10	(10%)	0		0	
- Orthostatic Hypotension	1	(2%)	0		0		0		3	(6%)	0		0		0		4	(4%)	0		0		0	
- Phlebitis	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Thrombophlebitis Superficial	1	(2%)	0		0		0		0		0		0		0		1	(<1%)	0		0		0	
- Thrombosis	1	(2%)	1	(2%)	0		0		1	(2%)	0		0		0		2	(2%)	1	(<1%)	0		0	

[a] Only the highest grade is included for patients who experienced a particular event more than once.