Four-Arm Randomized Phase II Study of SGI-110: 5 days, versus 10 days, versus 5 days + idarubicin, versus 5 days + cladribine, in Previously Untreated Patients ≥ 70 Years with Acute Myeloid Leukemia

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Short Title	4-Arm Randomized Phase II Study of SGI-110 in elderly AML
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1.0 Objectives

1.1 To determine the complete remission (CR) rate, remission duration, leukemia-free survival, and survival in patients ≥ 70 years with previously untreated AML with 4 different SGI-110 single agent and SGI-110 based combination regimens.

1.2 To determine the safety profile and tolerability of the 4 SGI-110 single agent and SGI-110 based combination regimens in patients ≥ 70 years of age with previously untreated AML.

2.0 Background

2.1 The Diseases

Acute myeloid leukemia (AML) accounts for approximately 25% of all cases of leukemia diagnosed in the Western hemisphere. It is a clonal myelopoietic stem cell disorder characterized by the accumulation of neoplastic cells in the bone marrow and in the peripheral circulation. Age-adjusted incidence ranges from 1 per 100,000 in people < 20 years to 10 per 100,000 in the elderly. Current induction chemotherapy protocols combining cytarabine and an anthracycline administered as first-line treatment induce complete remissions in a majority (55% to 75%) of patients. Standard consolidation therapy with high doses of cytarabine leads to improved survival. Between 50% and 70% of patients, however, can be expected to relapse, so that only about 30% attain long-term disease-free survival.

Age is a major factor that determines the prognosis of patients with untreated AML. The treatment of acute myeloid leukemia (AML) in older patients has not improved significantly in recent years when compared with the considerable progress that has been made in younger patients (1-3). AML occurring in patients ≥ 60 years of age continues to be associated with an extremely poor prognosis. Using a standard induction combination such as the “3+7” regimen (ara-C plus an anthracycline), the complete remission (CR) rate is 40% to 50%, the mortality 20% to 40%, and remission durations are usually transient and rarely last more than 12 months. The median time from treatment with the “3+7” regimen to death is 5 to 10 months and less than 10% of patients stay in remission at 3 years (4). Patients who are ≥ 70 years of age in particular tolerate 3+7 induction regimen very poorly with even worse results [20]). The reasons for this difference in outcome when compared to younger patients are multiple. Differences in the biology of AML in older patients is reflected by a higher proportion of patients with an unfavorable karyotype, a higher rate of primary drug resistance associated with overexpression of P-glycoprotein (P-gp), and an increased frequency of disease evolution from a preexisting and at time probably unrecognized myelodysplasia. Poorer tolerance of combination chemotherapy regimens leads to the use of less intensive treatment protocols (5). It is clear that several aspects of therapy in this group of patients require improvement. The development of new and effective anti-AML agents, however, remains a cornerstone of the continued efforts to improve the outcome of poor-prognosis patients. As the principal cause of treatment failure in older patients is resistant AML (manifested by short CR durations or failure to enter CR), investigational strategies should focus primarily on this problem and the introduction of new agents is warranted.

2.2 The Treatment - SGI-110 4-arm study

For the most updated SGI-110 clinical data, please refer to the most recent SGI-110 Investigators’ Brochure.

SGI-110 is a novel second generation hypomethylating agent which has been rationally synthesized to increase the half-life of its metabolite, decitabine, and to improve on the hypomethylation efficacy. SGI-110 has undergone completed Phase I studies. Phase 2 studies using SGI-110 60mg/m2 versus 90mg/m2 daily for 5 days are ongoing in newly diagnosed MDS and AML and in MDS salvage. SGI-110 60mg/m2 daily x 10 is undergoing evaluation in AML salvage. The results so far appear very encouraging demonstrating longer half-life of the decitabine metabolite, better hypomethylation capacity with SGI-110 compared with previous data with Dacogen (commercial decitabine), significant anti-MDS and anti-AML efficacy, and minimal side effects (6,7).

In a Phase I study, 78 patients (64 AML, 14 MDS) were enrolled in the dose escalation part: 44 patients in the daily x 5 regimen and 34 in the weekly x 3 regimen. There median age was 69 years. Median number of prior regimens was 3.

The PK profile demonstrated efficient conversion of SGI-110 to decitabine as predicted from the SGI-110 rational design, resulting in longer SGI-110 exposure window (beyond 8 hours) compared to Dacogen IV (3-4 hours). At SGI-110 dose range of 60-125 mg/m2, observed mean decitabine AUCs (88-231 ng*hr/mL) reach or exceed the therapeutic range seen with 20 mg/m2 Dacogen IV (115 ng*hr/mL) while achieving only a small fraction of the Cmax (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). SGI-110 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/m2; a plateau in maximum average hypomethylation (~25%) was evident at higher daily doses (90-125 mg/m2) and therefore the BED for the daily x 5 schedule is established at 60 mg/m2. The 25% average hypomethylation of LINE-1 compares favorably with that observed historically after Dacogen IV at the dose of 20 mg/m2 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/m2 daily and 60 mg/m2 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/m2 weekly x 3. With the daily regimen, 125 mg/m2 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 (14). Since the abstract publication, maximum hypomethylation was noted at the 60mg/m2 dose, while clinical MTD was defined at 90mg/m2 dose. Therefore the Phase II study proceeded to compare 60 versus 90mg/m2 daily for 5 days in newly diagnosed MDS and AML. A further arm investigated SGI-110 60mg/m2 daily x 10 days in AML salvage. Finally SGI-110 60mg/m2 daily x 5 is being evaluated in patients with MDS and progression on azacitabine/SGI-110 therapy (6).

The Phase II randomized study of the biologic effective dose 60mg/m2 daily x 5 and clinical Phase II dose 90mg/m2 daily x 5 is ongoing. As of June 30, 2013, sixty-seven patients (50 relapsed/refractory AML, 17 treatment naïve elderly AML) were treated and had a minimum follow up of 3 months. Patients were randomized to either 60 mg/m^2 dose (32 patients) or 90 mg/m^2 dose (35 patients). The median age was 66 years (range, 22–84), 69% were male, and ECOG PS of 0/1/2 was reported in 11/47/9 patients respectively. Median number of prior regimens was 2

(range, 0–10). Patients' characteristics were well balanced between the 2 dose groups. The primary endpoint of overall remissions (CR, CRp, or CRi) was observed in 17/67 patients (25% with 95% CI, 16–37%). There were 8 complete remissions (CR, CRp, or CRi) in 50 patients with relapsed/refractory AML (16% with 95% CI, 7-29%); and 9 complete remissions (CR, CRp, or CRi) in 17 treatment-naïve elderly AML patients (53% with 95% CI, 28-77%). Five patients (4 relapsed/refractory, and one treatment-naïve elderly AML) subsequently received a stem cell transplant. There was no difference in the complete remission rate between 60 and 90 mg/m^2 doses (8 remissions in 32 patients at 60 mg/m^2, and 9 remissions in 35 patients at 90 mg/m^2). LINE-1 DNA methylation data before and after treatment was available in 50 (75%) patients enrolled. LINE-1 demethylation ≥ 10% post treatment was observed in 83% and 78% in the 60 mg/m^2 and 90 mg/m^2, respectively. The median maximum LINE-1 demethylation for responders is 25% as compared to 19% for non-responders. The most common adverse events (AEs) regardless of relationship to SGI-110 ≥ Grade 3 include febrile neutropenia, thrombocytopenia, anemia, leukopenia, neutropenia, and pneumonia. The 90 mg/m^2 dose showed a greater frequency of Grade 3/4 related AEs ≥ 10% (anemia, febrile neutropenia, leukopenia, neutropenia, and thrombocytopenia) compared to the 60 mg/m^2 dose (7).

2.3 Rationale for the Proposed Regimen in Elderly AML

Up to 50 patients older than age 65 with newly diagnosed AML were treated in the previously described Phase II studies under 2.2. The early results are impressive in terms of CR and marrow CR rates. In our institutional experience, 9 of the first 12 patients treated achieved remissions. This is significant in this elderly AML population. We are therefore proposing an investigator initiated IND study to gain further experience with different SGI-110 regimens. This will help in the Phase III design of the potential FDA pivotal trial which will evaluate SGI-110 based therapy versus best standard of care in patients who cannot tolerate intensive chemotherapy. We will restrict the evaluation in the study to patients 70 years or older, since there is little argument that such patients do not benefit from intensive anti-AML therapy. Since we do not know whether 5 or 10 days of hypomethylator therapy is better, we propose to include 2 arms, one using single-agent SGI-110 60mg/m2 SQ daily x 5, and the second using SGI-110 60mg/m2 SQ daily x 10. We wish also to explore, in this pilot experience SGI combinations. Anthracyclines are historically effective in AML; therefore a third arm will evaluate SGI-110 60mg/m2 SQ daily x 5 with idarubicin at the low-dose 6mg/m2 daily x 2. Finally, cladribine, an old drug with single-agent efficacy in AML, was found to be an effective hypomethylating agent . Therefore combining SGI-110 with cladribine at low-doses may improve the anti-AML and hypomethylation efficacy. The fourth arm will combine SGI-110 60mg/m2 SQ daily x 5 with cladribine 3mg/m2 daily x 5.

2.4 Update of January 27, 2017

As of February 2017, 34 patients have been treated on study. The complete response in the 4 treatment arms are as follows: 4 out of 8 patients responded in the SGI-110 for 5 days arm; 5 out of 9 patients responded in the SGI-110 for 10 days arm; 7 out of 8 patients responded in the SGI+idarubicin arm and 3 out of 9 patients responded in the SGI+cladribine.

In addition, Astex, the sponsoring company, conducted a separate multi-institutional study of SGI-110 60mg/m2 for 5 and 10 days in older patients with newly diagnosed AML who were not candidates for intensive chemotherapy (8). A total of 103 patients were treated, 51 patients were treated on the 5-day and 52 patients were treated on the 10-day regimens. The characteristics of the 2 study groups were well-balanced. Overall the CR rates were 19/51 = 37% on the 5-day regimen and 16/52 = 31% on the 10-day regimen. The overall response rates were 57% and 48%, respectively. The median survival were 10.5 months on the 5-day regimen and 9.5 months on the 10-day regimen (p=0.70). Side-effects, including myelosuppression, were similar in the 2 study groups. The 60-days all-cause mortality was also similar between the two study groups.

The study concludes that both schedules (SGI-110 given in 5-day and SGI-110 given in 10-day) were similar (8).

Based on the above findings, and after discussion with the Biostatistical collaborators, Dr. Xuelin Huang and Graciela M. Nogueras-Gonzalez, it was decided to close the 2 arms of SGI-110 for 10 days (based on the Astex study)and SGI-110 + cladribine (low CR rate),and continue the study, with the same Bayesian statistical design, only in the 2 arms of SGI-110 for 5 days and SGI-110 +idarubicin.

3.0 Background Drug Information

3.1 SGI-110

Further information is available in the Investigator Brochure.

3.1.1 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. 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 decitabine. SGI- 110's activity was demonstrated with the same preclinical pharmacodynamic assays used to demonstrate decitabine's efficacy e.g., 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.

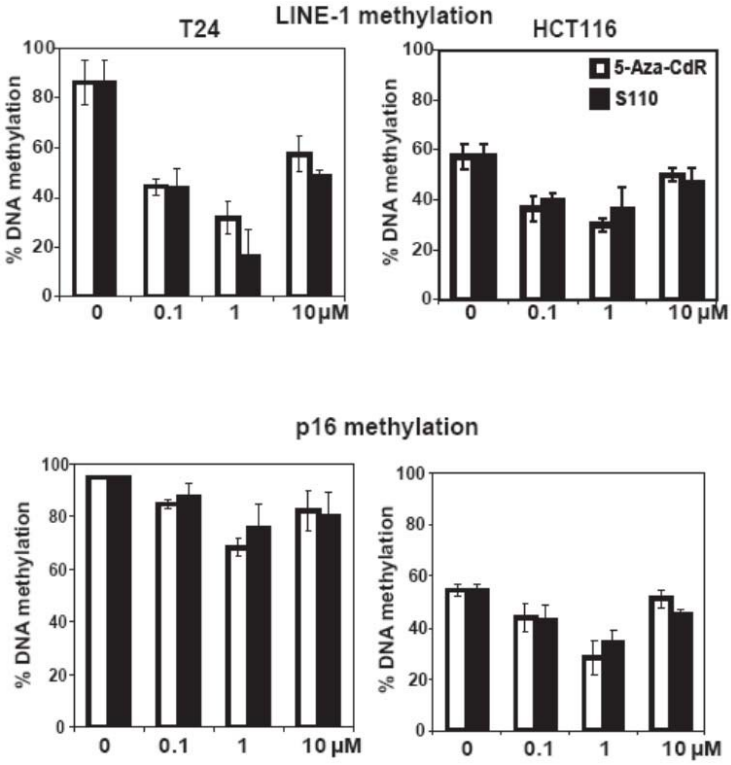
In vitro evidence suggests that SGI-110 has a longer half-life than decitabine in the presence of cytidine deaminase. Exploratory preclinical studies demonstrate that unlike decitabine, SGI-110 can suppress the polycomb repressor complex 2 which is involved in silencing tumor suppressor genes. These 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.

3.1.2 Summary of Nonclinical Data

a. 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 retro transposable 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). Both azacitidine and decitabine by itself have low objective response rates.

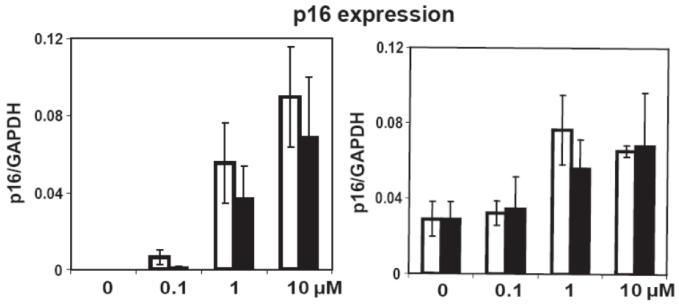
Figure 1: Effects of SGI-110 (filled bars) and decitabine (open bars) on LINE-1 and p16 Gene Methylation Levels in T-24 and HCT116 Cell Lines



In both T-24 and HCT116 cells, the decrease in the level of methylation was dose-dependent and comparable for SGI-110 and decitabine 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 treatments 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



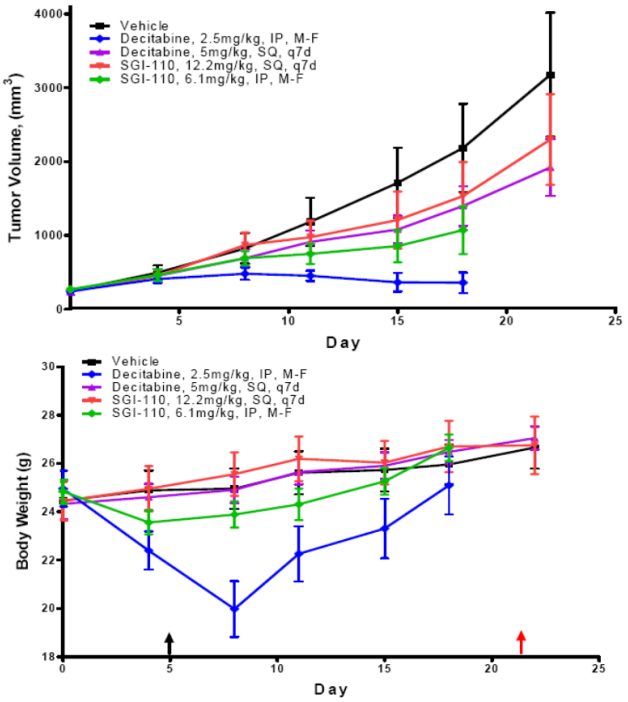
As shown in Figure 2, untreated T-24 bladder carcinoma cells do not express p16, and dose dependent

increases in p16 expression were observed after 6 days of continuous treatment with SGI-110 or decitabine. 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.

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, SGI-110 5 mg/kg administered subcutaneously every 7 days and 2.5 mg/kg administered intraperitoneally Monday to Friday. Equivalent doses and schedules of decitabine 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, SGI-110 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.

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



C. General Safety (Cardiac, CNS, and Respiratory)

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 (IC50) 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 unobserved-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.

3.1.3 Risks of SGI-110 single agent and combination with idarubicin

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.

Risks of idarubicin described below in the subsequent sections.

There is no available clinical data for the combination of SGI-110 with idarubicin but the only overlapping toxicity of all 3 agents is myelosuppression which should be well-monitored and managed during the first cycle. This is also why the study proposes the use of only a fraction of the commercially and clinically full doses of idarubicin in combination with the full dose of SGI-110.

3.1.4 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. SGI-110 is a new chemical entity that may possess enhanced pharmacokinetic or pharmacodynamic properties compared to SGI-110.

The activity of SGI-110 was demonstrated with the same preclinical pharmacodynamics assays used to demonstrate the activity of decitabine, e.g., 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.

3.2 Idarubicin

Idarubicin is commercially available. Please see package insert for further information.

Synonyms 4-Demethoxydaunorubicin; 4-DMDR, Idarubicin Hydrochloride, IDR: IMI30; NSC-256439, SC 33428

Use Treatment of acute leukemias (AML, ANLL, ALL), accelerated phase or blast crisis of chronic myelogenous leukemia (CML), breast cancer

Contraindications Hypersensitivity to idarubicin, other anthracyclines, or any component of the formulation; bilirubin >5 mg/dl; pregnancy

Warnings/Precautions The U.S. Food and Drug Administration (FDA) currently recommends that procedures for proper handling and disposal of antineoplastic agents be considered. Can cause myocardial toxicity and is more common in patients who have previously received anthracyclines or have pre-existing cardiac disease; reduce dose in patients with impaired hepatic function.
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.

Adverse Reactions
>10%

Cardiovascular: Transient EKG abnormalities (supraventricular tachycardia, S-T wave changes, atrial or ventricular extrasystoles); generally asymptomatic and self-limiting. Congestive heart failure, dose-related. The relative cardiotoxicity of idarubicin compared to doxorubicin is unclear. Some investigators report no increase in cardiac toxicity at cumulative oral idarubicin doses up to 540 mg/m^2; other reports suggest a maximum cumulative intravenous dose of 150 mg/m^2.

Central nervous system: Headache

Dermatologic: Alopecia (25% to 30%), radiation recall, skin rash (11%), urticaria

Gastrointestinal: Nausea, vomiting (30% to 60%); diarrhea (9% to 22%); stomatitis (11%); GI hemorrhage (30%)

Genitourinary: Discoloration of urine (darker yellow)

Hematologic: Myelosuppression, primarily leukopenia; thrombocytopenia and anemia. Effects are generally less severe with oral dosing

Nadir: 10-15 days
Recovery: 21-28 days

Hepactic: Elevations of bilirubin and transaminases (44%) 1% to 10%

Central nervous system: Seizures

Neuromuscular & skeletal: Peripheral neuropathy <1%: Hyperuricemia

Overdosage/Toxicology Symptoms of overdose include severe myelosuppression and increased GI toxicity. Treatment is supportive. It is unlikely that therapeutic efficacy or toxicity would be altered by conventional peritoneal or hemodialysis.

Drug Interactions Patients may experience impaired immune response to vaccines; possible infection after administration of live vaccines in patients receiving immunosuppressants

Stability Store intact vials of solution under refrigeration (2°C to 8°C/36°F to 46°F); protect from light. Solutions diluted in D_5W or NS for infusion are stable for 4 weeks at room temperature and 7 days under refrigeration.

Mechanism of Action Similar to doxorubicin and daunorubicin; inhibition of DNA and RNA synthesis by intercalation between DNA base pairs

Extravasation management: Topical cooling may be achieved using ice packs or cooling with circulating ice water. Cooling of site for 24 hours as tolerated by the patient. Elevate and rest extremity 24-48 hours, then resume normal activity as tolerated. Application of cold inhibits vesicant's cytotoxicity. Application of heat can be harmful and is contraindicated. If pain, erythema, and/or swelling persist beyond 48 hours, refer patient immediately to plastic surgeon for consultation and possible debridement.

4.0 Patient Eligibility

Inclusion:

4.1 Previously untreated AML patients, except those who have received prior therapy with hydroxyurea, single agent chemotherapy (e.g. decitabine), hematopoietic growth factors, biological or targeted therapies are allowed.
4.2 Age $\geq$ 70 years.
4.3 ECOG performance status ≤ 2.
4.4 Sign a written informed consent form.
4.5 Adequate liver function (total bilirubin $\leq$ 2mg/dL, SGPT or SGOT $\leq$ x 4 ULN) and renal function creatinine clearance of $\geq$ 50 mL/min (estimated by the Cockroft-Gault [C-G] formula).
4.6 Male patients must use an effective contraceptive method during the study and for a minimum of 8 weeks after study treatment.
4.7 Baseline LVEF >/= 40%.

Exclusion:

4.8 Patients with ≥ NYHA grade 3 heart disease as assessed by history and/or physical examination.

4.9 Patients who received more than one full course of prior hypomethylating agents azacitidine or decitabine

4.10 Have any other severe concurrent disease, or have a history of serious organ dysfunction or disease involving the heart, kidney, liver, or other organ system that may place the patient at undue risk to undergo treatment.

4.11 Patients with a systemic fungal, bacterial, viral, or other infection not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment).

4.12 Pregnant or lactating patients.

4.13 Any significant concurrent disease, illness, or psychiatric disorder that would compromise patient safety or compliance, interfere with consent, study participation, follow up, or interpretation of study results.

4.14 Any concurrent malignancy (with the exception of exclusion # 4.15)

4.15 Exceptions to # 4.14: a) Patients with treated non-melanoma skin cancer, in situ carcinoma, or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible for this study if definitive treatment for the condition has been completed; b) Patients with organ-confined prostate cancer with no evidence of recurrent or progressive disease based on prostate-specific antigen (PSA) values are also eligible for this study if hormonal therapy has been initiated or a radical prostatectomy has been performed.

5.0 Treatment Plan

5.1 Schedule

Patients are randomized between 2 treatment arms:

Induction:

A) SGI-110 60mg/m2 subcutaneously (SQ) daily x 5
B) SGI-110 60 mg/m2 SQ daily x 5 + idarubicin 6mg/m2 IV daily x 2

Cycles will be repeated every 4 to 6 weeks or longer as indicated by leukemia recurrence or recovery of normal hematopoiesis. Since efficacy from epigenetic treatment with agents such as SGI-110 may take longer to manifest, it is recommended that patients receive at least 2 courses of the above regimens regardless of their response.

If a patient does not achieve a CR or CRi after a maximum of 3 induction courses, the patient will be taken off study unless the patient is deriving clinical benefit at which time continuation of protocol therapy will be allowed with prior PI approval.

Maintenance:

Patients who achieve a CR or CRp during induction may receive up to 24 months of maintenance therapy every 4 to 8 weeks. The maintenance arm will be the same as the induction arm e.g. patients who are induced on on SGI-110 + idarubicin are also maintained with SGI-110 + idarubicin.

A) SGI-110 60mg/m2 SQ daily x 5
B) SGI-110 60mg/m2 SQ daily x 5 + idarubicin 6 mg/m2 IV on Day 1

- Patient may receive follow up laboratory tests from their local physician.
- All protocol-specific treatment decisions will be made by MD Anderson physician.
- The PI/treating physician must review all outside lab results, determine the clinical significance and sign/date the report.

5.2 Dose Modifications

Induction:

If a second induction course is considered, doses of each drug should be reduced by 25% for grade 3 drug-related non-hematological toxicities. Doses should be reduced by 50% for grade 4 drug-related non-hematological toxicities and/or life-threatening infections.

Maintenance:

Prior to each maintenance cycle, the ANC should be $\geq$ 1.0 x 10^9/L and the platelet count $\geq$ 60 x 10^9/L, except for patients who are considered to have achieved a CRp following induction and in whom a platelet count of < 60 x 10^9/L will be allowed to continue. In addition, any nonhematological toxicity experienced by the patient must return to $\leq$ grade 2 or baseline before the patient continues treatment with the study drugs. Doses missed or held during a cycle of treatment will not be made up and are recorded as being omitted. If a patient experiences multiple toxicities, dose adjustments will be based on the most severe toxicity.

Doses of SGI-110 and idarubicin may be reduced according to the following criteria:
- grade 3-4 (severe) drug-related nonhematologic toxicities (including life-threatening infections), or prolonged myelosuppression (hypocellular marrow [<10%] and failure to recover the absolute neutrophil count [ANC] ≥1,000 and platelet count ≥ 60,000 by day 42): reduce both drugs by 25-33% as per Table below.

Dose level	**SGI-110**		**Idarubicin**
Start-0	60mg/m2		6mg/m2
-1 level	45mg/m2		4mg/m2
-2 level	30mg/m2		3mg/m2

~~Once doses have been reduced for drug-related non-hematologic toxicities, they should not be increased later on unless it is decided that the toxicity has completely resolved, was not drug-related, or that the benefit outweigh the risk.~~

Dose reductions are not necessary for alopecia, drug-related fever, fatigue, electrolyte abnormalities, or nausea/vomiting that can be controlled with supportive care measures. Left Ventricular Ejection Fraction should be done to monitor for congestive heart failure in patients receiving idarubicin following induction. .

All other dose modifications outside the above mentioned suggestions and which are considered to be in the best interest of the individual patient should be discussed with the Principal Investigator.

In general, in the combination arms, if those reductions are necessitated as described above, the doses of idarubicin may be reduced without reducing the SGI-110 doses.

Dose reductions other than the above may be considered if judged to be in the best interest of the patient. These include reductions in the number of days of SGI-110 or idarubicin if judged indicated, such modifications must however be discussed with and approved by the primary investigator.

All drug dose modifications will be clearly documented in the medical record to verify compliance with the protocol.

5.3 Concomitant Therapy

Necessary supportive measures for optimal medical care will be given throughout the study as determined by the treating physician and the patient's medical need. No concomitant chemotherapy (with the exception of prophylactic intrathecal therapy), immunotherapy, or therapy with monoclonal antibodies will be allowed during this study. Investigational agents that are not used for treatment of the leukemia per se (e.g. anti-infective prophylaxis or therapy) will be allowed. No concomitant medications will be captured as part of the protocol data.

Use of a colony-stimulating factor (e.g., G-CSF, GM-CSF, or erythropoietin) is at the discretion of the treating physician and is permitted if judged in the patient's best medical interest.

Prophylactic antibiotics, antifungals, and antiviral agents (e.g., levofloxacin, itraconazole, valacylovir, etc.) are recommended; however, the use of these or other drugs will be left to the treating physician's discretion.

6.0 Pretreatment evaluation

History and physical, CBC with differential and platelets, Chemistry profile (at least creatinine, SGOT or SGPT, total bilirubin) within 14 days of therapy start.

Bone marrow aspirate and/or biopsy within 30 days of therapy start. The bone marrow evaluation will include cytogenetic studies, if not done in previous 3 months.

Pregnancy (urine or blood) test for women of childbearing potential within two weeks of start of therapy. Child bearing potential is defined as not post-menopausal for 12 months or no previous surgical sterilization.

Baseline LVEF.

7.0 Evaluation during Study

On Day 1 (+/- 7 days) of every cycle, the following tests and procedures will be performed:

- You will have a physical exam, including measurement of your weight
- Vital signs.
- Your performance status will be recorded.

CBC with differential and platelet counts at least once a week until remission, then every 2 to 4 weeks during therapy, and every 4 to 8 weeks thereafter as long as on study. No differential is needed if the WBC is < 1.0 x 10^9/L.

Chemistry profile (at least creatinine, SGOT or SGPT, total bilirubin) at least weekly until remission, then every 4 to 8 weeks during therapy.

Bone marrow aspirate and/or biopsy starting on day 28 (± 7 days) of therapy and then every 2 weeks (± 7 days) as required by leukemia evolution until remission or non-response. Bone marrow tests can be ordered more frequently if mandated by development of peripheral blood counts. No repeat bone marrow is necessary if non-response or progressive disease can be unequivocally diagnosed from peripheral blood tests, or, in patients with a WBC ≤ 0.3 if the bone marrow test is considered non-contributory by the investigator at any time point (±2 days).

LVEF every 3-4 cycles as indicated.

Optional. Blood 10cc pre-treatment, on Days 1 and 15 (+/- 2 days) of the first course to evaluate epigenetic modulation. (This will cover both the 5-day and 10-day regimens)

Follow-up Visits

After your last dose of study drug (after completion of all therapies), you will have follow-up visits. You will only have these visits if the disease has responded to the study drug. This can be done at home through your local cancer doctor as indicated (usually visit + routine CBC and chemistries every 2-3 months). Approximately every 6 months, you will return to Houston for a physical exam and blood (about 1 tablespoon) will be drawn for routine tests:

Chemistry profile (at least creatinine, SGOT or SGPT, total bilirubin).

8.0 Criteria for Response

8.1 Complete Remission (CR):

. Neutrophil count ≥ 1.0 x 10^9/L and platelet count ≥ 100 x 10^9/L, and normal bone marrow differential (≤ 5% blasts)

8.2 Complete Remission without blood count recovery (CRi): Peripheral blood and bone marrow results as for CR, but with platelet counts of < 100 x 10^9/L or ANC < 1.0 x 10^9/L

8.3 Partial Remission (PR):
Blood count recovery as for CR, but with both a decrease in marrow blasts of at least 50% and not more than 6 to 25% abnormal cells in the marrow.

8.4 Early mortality: Death within 14 days of first dose.

8.5 Patients who achieve a CR or CRp during induction may receive up to 24 months of maintenance therapy every 4 to 8 weeks

8.6 Prior to each maintenance cycle, the ANC should be $\geq$ 1.0 x 10^9/L and the platelet count $\geq$ 60 x 10^9/L, except for patients who are considered to have achieved a CRp following induction and in whom a platelet count of < 60 x 10^9/L will be allowed to continue.

9.0 Criteria for Discontinuation of Therapy

Patients can be discontinued from the study under the following conditions:

9.1 Patient's physician considers a change of therapy would be in the best interest of the patient.
9.2 Patient requests discontinuation or withdraws consent.
9.3 There is unacceptable toxicity (e.g., grade 4 nonhematologic toxicity), not controlled with dose adjustments.
9.4 There is a need for any treatment not allowed by the protocol.
9.5 Investigator determines that the patient has progressive disease after sufficient induction therapy.

Every 6 months, you will return to Houston for a physical exam and blood (about 1 tablespoon) will be drawn for routine tests.

10.0 Statistical Considerations

10.1.1 Update of the General Description/Sample Size February 01, 2017

This is a Phase II with 2 parallel arms study of SGI-110 in patients with newly diagnosed AML >/= 70 years of age. The primary objective is to obtain an initial assessment of efficacy for the two SGI-110 regimens in this patient group:

1) SGI-110 single-agent for 5 days.
2) SGI-110 for 5 days combination with idarubicin for 2 days.

For each arm, we will enroll 20 patients. When all the arms have 20 patients then to be able to enroll more patients after the first 20 patients they have to satisfy the following rules: 1) there is more than 95% chance that the grade 3-4 non-hematological toxicity rate doesn't exceed 30%. 2) there is less than 10% chance that the 8-week mortality exceeds 15% and 3) there is more than 2.5% chance that the CR rate (CR+CRi) is more than 30%.

The arm or arms with the satisfying monitor rules above will continue to enroll an additional 20 patients. This will be decided through an interim analysis discussion with the Leukemia experts and the modality experts coordinating the study.

Complete Remission monitoring

The primary endpoint is the complete remission rate (CRR) evaluated after at least 2 cycles but would also be evaluated after 4 and 6 cycles if the patient is stable or improving. We have a target CRR of 30%, while a CRR of 15% is considered unacceptable. We will monitor complete remission using the Bayesian approach of Thall et al. [**19]**.The probability of complete remission

is denoted by P_{CR}. We assume P_{CR} ~ beta (0.6, 1.4). Our stopping rule is given by the following probability statement: Pr (P_{CR} > 0.30 | data) < 0.025. That is, we will stop the study if, at any time during the study, we determine that there is less than 2.5% chance that the CRR is more than 30%. This stopping rule will be applied in each arm. The stopping boundaries for complete remission, based on these assumptions and monitoring conditions are found in **Table 1**. We will apply these stopping boundaries starting from the first patient and in cohorts of 10. For example, accrual will cease if only 2 patients experiences complete remission among in the first 20 patients treated. The operating characteristics are summarized in **Table 2.** Both the decision rule and operating characteristics were calculated using the stopbound procedure in Stata version12.1.

Table 1. Stopping boundaries for Complete Remission (separately for each arm)

The number of patients evaluated for complete remission	10	20	30	40
The number of patients with complete remission	0	</=2	</=4	</=6

Table 2. Operating characteristics for Complete Remission (separately for each arm)

True Complete Remission Rate	Early Stopping Probability	Sample Size		
		25th percentile	Median	75th percentile
0.15	0.5994	20	30	40
0.20	0.3303	30	40	40
0.25	0.1528	40	40	40
0.30	**0.0670**	40	40	40
0.35	0.0255	40	40	40
0.40	0.0087	40	40	40

Toxicity Monitoring

We will monitor toxicity using the Bayesian approach of Thall et al. [**19**]. **A toxicity is defined as grade 3 or higher non-hematological toxicity occurring during the first two cycles.** Following are the rules for the monitoring of toxicities. The probability of toxicities is denoted by P_T. We assume P_T ~ beta (0.6, 1.4). Our stopping rule is given by the following probability statement: Pr (P_T > 0.30 | data) > 0.95. That is, we will stop the study if, at any time during the study, we determine that there is more than 95% chance that the toxicity is more than 30%. This stopping rule will be applied in each arm. The stopping boundaries for toxicities, based on these assumptions and monitoring conditions is found in **Table 3**. We will apply these stopping boundaries starting from the first patient and in cohorts of 5. For example, accrual will cease if 4 patients experiences toxicities among in the first 5 patients treated. The operating characteristics are summarized in **Table 4.** Both the decision rule and operating characteristics were calculated using the stopbound procedure in Stata version12.1.

Table 3. Stopping boundaries for Toxicities (separately for each arm)

The number of patients evaluated for toxicities	5	10	15	20	25	30	35	40
The number of patients with toxicities	4	6	8	10	12	14	16	18

Table 4. Operating characteristics for Toxicity Monitoring (separately for each arm)

True Toxicity Rate	*Early*	Sample Size

	Stopping Probability	25th percentile	Median	75th percentile
0.10	*0.0005*	40	40	40
0.20	*0.0149*	40	40	40
0.30	***0.1247***	40	40	40
0.40	*0.4581*	15	40	40
0.50	*0.8272*	10	15	40

Mortality Monitoring

We will monitor 8-week mortality using the Bayesian approach of Thall et al. [**19]**. Following are the rules for the monitoring of 8-week mortality. The probability of 8-week mortality is denoted by P_M. We assume P_M ~ beta (0.3, 1.7). Our stopping rule is given by the following probability statement: Pr (P_M > 0.15 | data) > 0.90. That is, we will stop the study if, at any time during the study, we determine that there is more than 90% chance that the 8-week mortality is more than 15%. This stopping rule will be applied in each arm. The stopping boundaries for 8-week mortality, based on these assumptions and monitoring conditions is found in **Table 5**. We will apply these stopping boundaries starting from the first patient and in cohorts of 5. For example, accrual will cease if 3 patients died during the first 8 weeks among in the first 5 patients treated. The operating characteristics are summarized in **Table 6**. Both the decision rule and operating characteristics were calculated using the stopbound procedure in Stata version12.1.

Table 5. Stopping boundaries for Mortality (separately for each arm)

The number of patients evaluated for mortality	5	10	15	20	25	30	35	40
The number of patients died during the first 8 weeks	3	4	5	6	7	8	9	10

Table 6. Operating characteristics for Mortality Monitoring (separately for each arm)

True Mortality Rate	Early Stopping Probability	Sample Size		
		25th percentile	Median	75th percentile
0.05	0.0029	40	40	40
0.10	0.0298	40	40	40
0.15	**0.1552**	40	40	40
0.20	0.3790	20	40	40
0.25	0.6341	10	25	40

Statistical Analysis Plan

All patients who received at least 1 dose of the agent will be included in the intent-to-treat analysis for efficacy and safety. Demographic/clinical characteristics and safety data of the patients will be summarized using descriptive statistics such as mean, standard deviation, median and range (i.e. remission duration). Complete remission rates (CRR) will be presented with 95% confidence intervals. The association between CRR and patient and clinical characteristics will be

examined by Wilcoxon's rank sum test or Fisher's exact test. Survival time will be estimated using the Kaplan-Meier method. Patients who drop out of the study will be included in the time to event data as "censored data". The two-sided log-rank test will be used to assess the differences of time to events between groups.

10.2 Treatment Assignment and Stopping Rules

Patients will be assigned to receive either of the 2 regimens. The randomization will be balanced 1:1 to each of the treatment arms.

11.0 Reporting Requirements

11.1 See Appendix C for guidelines for reporting ADR's to the IRB.

Adverse events will be graded using CTCAE version 4.03 (Appendix D)
The investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.
Adverse events and protocol specific data will be entered into PDMS/CORe. PDMS/CORe will be used as the electronic case report form for this protocol.
This study will be monitored by the MD Anderson IND Office and a protocol-specific monitoring plan will be followed.

Study Drugs

The Investigator is responsible for ensuring the study drugs are administered or dispensed only to subjects enrolled in the study. The Investigator will ensure that any used and unused vials of study drug and other study material will be destroyed locally (by our research pharmacy) or returned to the Sponsor on completion of the study.

Serious Adverse Event Reporting (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.**

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution **(**within 5 working days of knowledge of the event**)**.

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- **Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.**

- **Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**

- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.**

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Investigator Communication with Supporting Companies:

11.2 **Reporting to Astex Drug Safety**. The Sponsor-Investigator will notify Astex, as designated holder of the global safety database, of any Serious Adverse Event (SAE), pregnancy, or infant exposure, including those events reported to the Sponsor-Investigator by his/her Investigators, whether related to Study Drug or not, within twenty-four (24) hours of being made aware of the SAE. Such notification will

be provided to Astex by faxing the information contained in the exemplar Serious Adverse Event Report Form, which is appended to the Protocol, to the Astex Drug Safety Department

Astex Drug Safety SAE Reporting Fax Number
Local Fax: 925-551-3226
North America Toll-Free Fax: 800-576-6568

A copy of the correspondence sent to the FDA [or other controlling regulatory authority] shall be sent within twenty-four (24) hours to Astex Regulatory Affairs by email or fax:

Astex Regulatory Affairs email: david.smith@astx.com
Astex Regulatory Affairs Fax Number: 925.551.6491

Disputed SAEs. Even if the Sponsor-Investigator decides not to report an event, Astex may make its own determination that it is a reportable Serious Adverse Event, and may report it.

Reporting to FDA. The Sponsor-Investigator shall be responsible for notifying the FDA [or other controlling regulatory authority] within fifteen (15) calendar days, or seven (7) calendar days if fatal or life threatening, or according to local requirements if the local requirements are more strict, of any and all events that are both Serious and Unexpected Adverse Events and that are considered related to the Study Drug, including those events reported to the Sponsor-Investigator by Investigators from his/her Participating Centers.

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