ABST # A190

In Vivo Activity of SGI-110, a Novel Hypomethylating Agent for Treatment in Hematology and Solid Malignancies

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ABSTRACT

SGI-110 is a second generation hypomethylating agent being developed for treatment in myelodysplastic syndrome (MDS) and solid tumor malignancies. In previous work, SGI-110 has demonstrated potent in vivo activity in a number of tumor types, including non-hematological cell lines. Current efforts are underway to optimize formulation and delivery of SGI-110 for first-in-human (FIH) studies.

In animals, SGI-110 is well-tolerated across multiple species utilizing multiple routes of drug delivery. Tolerability studies have been performed in mouse, rat, and rabbit models with multiple dose routes and schedules. Myelosuppression is an observed toxicity endpoint for hypomethylating agents. Hence, myelotoxic effects were investigated by comparing RBCs and bone marrow cellularity of mice treated with and without SGI-110. Mice dosed with SGI-110 for five consecutive days showed a significant decrease in RBCs at the end of the dosing period and a continued decrease one week after dosing. Bone marrow cellularity also showed a decrease at the end of dosing, but recovered to near normal levels one week later. Interestingly, RBCs from SGI-110 treated mice were elevated in the bone marrow after the dosing period. Pyrosequencing methylation analysis of colon samples was also evaluated in this study. A significant decrease in B1 methylation was observed in colon samples of treated mice, indicating global DNA methylation is being inhibited. Decreased levels in several hematology parameters and decreases in bone marrow cellularity were also observed in rat and rabbit studies after five consecutive days of SGI-110 dosing. Increased dosing frequency, while maintaining the same total dose per week, appears to result in increased toxicity.

Previous pharmacokinetic studies have shown that SGI-110 rapidly metabolizes to decitabine, an FDA-approved drug for MDS. Multiple formulations and different routes of delivery were examined to determine the optimal dose form to be used in FIH studies. Subcutaneous dosing results in bioavailability that is similar to that of intravenous dosing. Subcutaneous dosing appears to reduce the C_{max} while maintaining similar AUC values when compared to intravenous dosing. Similar results in pharmacokinetic parameters are observed when the delivery vehicle is changed from an aqueous to non-aqueous formulation.

SGI-110 is a novel hypomethylating agent that is well-tolerated in rodent models, provides excellent PK exposure, and demonstrates inhibition of DNA methylation in a mouse model.

SGI-110 Structure

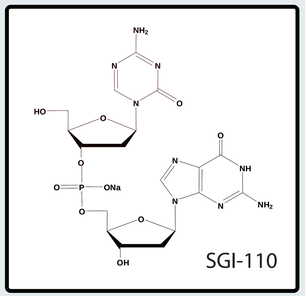

Figure 1: Structure illustrates incorporation of 5-aza-2'-deoxycytidine (red) into a guanine dinucleotide (black) to generate the second generation decitabine agent called SGI-110.

Bone Marrow Cellularity in SGI-110 Treated Mice

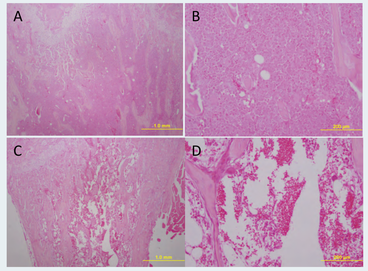

Figure 3: CD-1 mice were treated with vehicle or SGI-110 for 5 days. Femurs were harvested and fixed at Days 5. A) Vehicle for 5 days, 4X magnification; B) Vehicle for 5 days, 20X; C) SGI-110 for 5 days, 4X; D) SGI-110 for 5 days, 20X.

Methylation in Mouse Colon

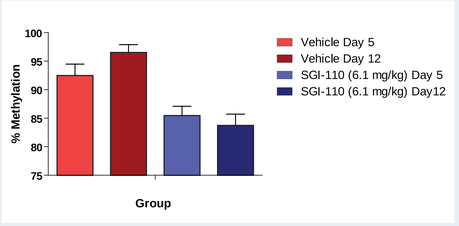

Figure 5: Average B1-methylation in mouse colon samples. CD-1 mice were treated with vehicle or SGI-110 for 5 days. Colon samples were harvested at Days 5 and 12. DNA recovered from the colon samples were processed for DNA methylation analysis.

Rat PK of Aqueous or Non-Aqueous Dosing

	Dose, Route	Vehicle	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{all} (ng*h/mL)
SGI-110	15 mg/kg SQ	Aqueous	0.1	0.2	663	246
SGI-110	15 mg/kg SQ	Non-Aqueous	0.4	0.4	123	136
Decitabine from SGI-110	6.1 mg/kg SQ	Aqueous	3.7	0.5	3740	18398
Decitabine from SGI-110	6.1 mg/kg SQ	Non-Aqueous	3.7	2.0	2268	15915

Table 2: Comparison of rat PK parameters from subcutaneous dosing of SGI-110 in aqueous and non-aqueous formulations .

CBC Analysis of SGI-110-treated Mice

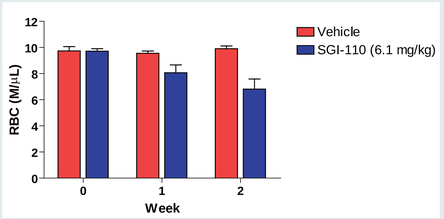

Figure 2: Average RBC levels from CD-1 mice treated with vehicle or SGI-110 for 5 days. CBC samples were harvested at Days 5 and 12.

Methylation in Mouse Whole Blood

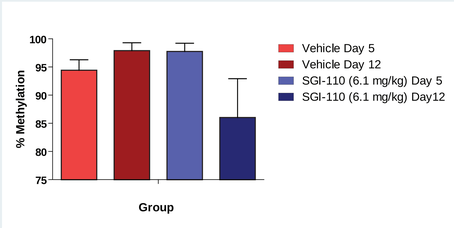

Figure 4: Average B1-methylation in mouse whole blood samples. CD-1 mice were treated with vehicle or SGI-110 for 5 days. Whole blood samples were harvested at Days 5 and 12. DNA recovered from the blood samples were processed for DNA methylation analysis.

Rat PK After Intravenous or Subcutaneous Dosing

	Dose, Route	Vehicle	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{all} (ng*h/mL)	Bioavail (%)
SGI-110	24.4 mg/kg IV	PBS	0.1	0.02	2593	224	-
SGI-110	24.4 mg/kg SQ	PBS	0.2	0.3	227	104	47
Decitabine from SGI-110	10 mg/kg IV	PBS	3.5	0.02	4727	14342	-
Decitabine from SGI-110	10 mg/kg SQ	PBS	3.4	1.0	2497	13653	95

Table 1: Comparison of rat PK parameters from intravenous and subcutaneous dosing of SGI-110 in an aqueous formulation.

CONCLUSIONS

- SGI-110 in mice resulted in myelosuppression as observed by decreases in RBCs and bone marrow cellularity.
- SGI-110 in mice resulted in global inhibition of DNA methylation as observed in both whole blood and colon samples.
- Subcutaneous dosing of SGI-110 results in high bioavailability of both SGI-110 and decitabine. When compared to intravenous dosing, AUC levels are comparable while C_{max} values are decreased.
- When compared to an aqueous formulation, a new non-aqueous formulation of SGI-110 has comparable AUC levels while C_{max} values are decreased.
- SGI-110 is a promising candidate for treatment of MDS, AML, and solid tumors.