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

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 5methylcytosine was observed in colon samples of treated mice, indicating global DNA methylation is being decreased. Decreased levels in several hematopoietic 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 comparable while Cmax values are decreased. When compared to intravenous dosing, AUC levels are comparable while Cmax values are decreased. Rat PK after intravenous or subcutaneous dosing of SGI-110 in mice resulted in myelosuppression as observed by decreases in RBC 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 both of SGI-110 and decitabine. When compared to intravenous dosing, AUC levels are comparable while Cmax values are decreased. When compared to an aqueous formulation, a non-aqueous formulation of SGI-110 has comparable AUC levels while Cmax values are decreased.

CONCLUSIONS

- SGI-110 in mice resulted in myelosuppression as observed by decreases in RBC 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 both of SGI-110 and decitabine. When compared to intravenous dosing, AUC levels are comparable while Cmax values are decreased.
- SGI-110 is a promising candidate for treatment of MDS, AML, and solid tumors.