SGI-110, a Novel Second Generation Potent DNA Methylation Inhibitor, In Development for the Treatment of MDS and AML. Preclinical Safety, Pharmacokinetics, and DNA Methylation Results of a Low Volume Subcutaneous (SC) Formulation

Abst. #31984

Jason Scholl[1], Rajashree Joshi-Hangal[2], Roger Inloes[2], Chongtie Shi[2], Pietro Taverna[3], Gavin S. Choy[3], Sanjeev Redkar[2] and Mohammad Azab[3]

[1]SuperGen, Salt Lake City, UT; [2]SuperGen, Pleasanton, CA; [3]SuperGen, Inc., Dublin, CA

Abstract

SGI-110, is a novel second generation DNA methylation inhibitor that is currently in Phase I/II clinical study for treatment of myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). SGI-110 is a dinucleotide of decitabine and guanosine developed to be more biologically stable than decitabine by making it less prone to deamination by cytidine deaminase, thus offering a promising alternative to current hypomethylating agents approved in MDS. SGI-110 demonstrated potent activity in vivo using different routes of administration (Chuang JC, et al, Mol Cancer Ther, 2010; 9:1443-50).

We report here the results of a novel SGI-110 non-aqueous formulation intended for clinical use. The clinical formulation can be administered in small volumes subcutaneously (SC) up to a concentration of 100 mg/mL. We evaluated 2 regimens: daily SC x 5 days (in rats, and rabbits); and weekly SC (once weekly in rabbits, and cynomolgus monkeys; and twice weekly in rats). Both regimens are intended for 28-day cycles.

The 5-day regimen was well tolerated up to a dose of 1.5 mg/kg/day x 5 in the most sensitive species (rabbit) which is equivalent to 18 mg/m^2/day x 5 in humans. The weekly regimen was also well tolerated up to 1.5 mg/kg weekly x 3 in rabbits, and up to 3 mg/kg weekly x 3 in monkeys (equivalent to 36 mg/m^2 weekly x 3 in humans). Rats tolerated much higher doses (30 mg/kg/day x 5; and 20 mg/kg twice weekly x 4 weeks). The main toxicity was myelosuppression in all species. The relative bioavailability of SGI-110 dosed SC is close to 100%. In vivo, SGI-110 rapidly converts to decitabine in rats, and rabbits, with much slower conversion in monkeys compared to other species, possibly sustaining efficacy for longer duration. Dose proportional pharmacokinetics and no significant accumulation of both SGI-110 and decitabine levels were evident after SC treatment in both the 5-day and the weekly regimens. We studied changes in LINE-1 DNA methylation in rats and monkeys after SGI-110 SC administration. Changes in LINE-1 DNA methylation after SGI-110 SC weekly x 4 in rats at tolerated doses of 12.5, 25 and 30 mg/kg/week were evident during the first recovery week (Day 31) and were dose-dependent. Maximum methylation reduction was observed with 30 mg/kg/week of SGI-110. These data in rats suggest a delayed pharmacodynamic effect.

In monkeys, SGI-110 was administered at 3 mg/kg/week SC for 3 weeks (Days 1, 8 and 15). Reduction in LINE-1 DNA methylation became evident by Day 8, reached a maximum reduction of 10-15% by Day 15-22, and was maintained until Day 29.

LINE-1 methylation levels were significantly reduced from baseline levels ($p < 0.05$) from Days 8-29. On Day 1, an average C_{max} of 33.4 ng/mL at a T_{max} of 1 hr and AUC of 120 ng*hr/mL were achieved for decitabine compared to Cmax of 184 ng/mL at a T_{max} of 1 hr and AUC of 381 ng*hr/mL for SGI-110. On Day 15, an increase in the average SGI-110 AUC to 592 ng*hr/mL was observed suggesting some accumulation. All other pharmacokinetic parameters for decitabine and SGI-110 were similar to those on Day 1. Compared to other animal species tested, levels of SGI-110 were consistently and substantially higher in monkey plasma across studies. SGI-110 was well tolerated in monkeys at this dose with only mild reversible myelosuppresion and no deaths.

In conclusion, based on the non-human primate monkey data, this uniquely developed low volume non-aqueous SC formulation of SGI-110 may allow sustained efficacy with less frequent weekly dosing offering a new alternative to MDS and AML patients. SGI-110 is being studied in a first-in-human study. This study is a randomized Phase I/II, dose escalation, multicenter study of two subcutaneous regimens (daily on Days 1-5, and weekly x 3 on Days 1, 8, 15, both given in a 28-day cycle) in relapsed or refractory MDS, and relapsed, refractory, or elderly AML patients.

SGI-110 Product for SQ Delivery

- A two vial kit - "Ready to reconstitute" product. Contents of the two to be mixed well prior to administration.
- Non-aqueous diluent using GRAS (generally recognized as safe) excipients present in commercially available formulations
- High concentration (up to 100 mg/mL) allows for low volumes of injection.
- Reconstituted solution stable for over 1 month under refrigerated conditions
- Vehicle is well tolerated in rodents and non-rodents

Two vial kit - SGI-110 powder and diluent

Diluent added to SGI-110 powder to make up to 100 mg/mL solution

Stable solution formed

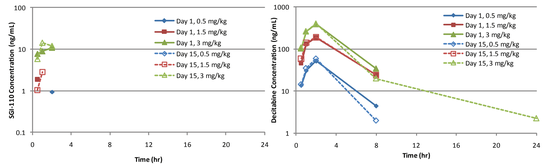
SGI-110 in Rabbits: Safety

Species	Dosing schedule	Dose levels/ # of animals	Tolerability	Necropsy results
Rabbit	Once/wk for 3 wks, 3 wks recovery	0, 0.5, 1.5, 3 mg/kg 10 animals/dose level	MTD* and HNSTD** at 1.5 mg/kg (18 mg/m^2). One animal died at 3 mg/kg during recovery. Dose-dependent effects on leukocytes, platelets, lymphocytes, erythroid parameters at ≥ 1.5 mg/kg. Recovery: Hematology effects nearly fully resolved at 1.5 and 3 mg/kg groups	Terminal: decreased thymus weight at 3 mg/kg; thymus and bone marrow depletion at ≥ 1.5 mg/kg. Recovery: full resolution of thymus and bone marrow depletion.
Rabbit	Daily for 5 days, 3 wk recovery	0, 1.5, 3.5, 7 mg/kg 10 animals/dose level	MTD* and HNSTD** at 1.5 mg/kg (18 mg/m^2). Mortality at 3.5 and 7 mg/kg. Dose-dependent effects on leukocytes, platelets, lymphocytes, erythroid parameters and mild decrease in red cell mass. Effects partially to fully resolved at recovery for 1.5 mg/kg	Terminal: decreased thymus weight; thymus and bone marrow depletion. Recovery (1.5 mg/kg): full resolution of bone marrow, partial resolution of thymus depletion. Died on study animals: thymus and bone marrow depletion; secondary inflammation/septicemia; hemorrhage.

* MTD: Maximum Tolerated Dose
** HNSTD: Highest Non-Severe Toxic Dose

PK of SGI-110 and Decitabine: Rabbits

SGI-110 Weekly, SQ



- TK curves of SGI-110 and derived decitabine from rabbits on Days 1 and 15
- SGI-110 disappears rapidly as it converts to decitabine over 24 hr
- No significant accumulation for SGI-110 or decitabine
- Plasma concentrations and exposures increased with increasing dose

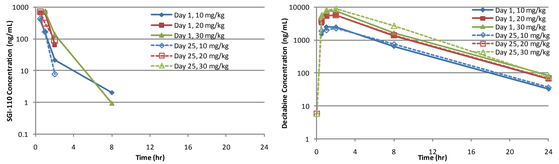
SGI-110 in Rats: Safety

Species	Dosing schedule	Dose levels/ # of animals	Mortality	Hematology results	Necropsy results
Rat	Twice/wk for 4 wks, 2 wks recovery	0, 10, 20, 30 mg/kg 30 animals/dose level	Mortality limited to the 30 mg/kg dose group	Dose-dependent effects on leukocytes, platelets, erythroid parameters and red cell mass; all effects near complete resolution in 10 and 20 mg/kg groups at recovery	Terminal: decreased thymus, testes, and epididymal weights; thymus and bone marrow depletion Recovery: thymus decrease less pronounced; bone marrow findings almost completely resolved; testes weights remained decreased
Rat	Daily for 5 days, 3 wk recovery	0, 5, 10, 20 mg/kg 30 animals/dose level	No test article-related deaths	Dose-dependent effects on leukocytes, platelets, erythroid parameters and red cell mass; all effects near complete resolution with reticulocytes elevated at recovery	Terminal: decreased thymus (all test groups) and uterus weight (20 mg/kg); thymus and bone marrow depletion Recovery: thymus and uterus findings resolved; bone marrow findings almost completely resolved

5-Day STD10 ≥ 20 mg/kg/day (120 mg/m^2/day)
Twice-weekly STD10 = 30 mg/kg/day (180 mg/m^2/day)
STD = Severely Toxic Dose

PK of SGI-110 and Decitabine: Rats

SGI-110 Twice Weekly, SQ



- TK curves of SGI-110 and derived decitabine from rats on Days 1 and 25
- No significant accumulation was observed for SGI-110 or decitabine
- Plasma concentrations and exposures increased with increasing dose
- Changes in LINE-1 methylation levels observed after once weekly dosing (data not shown)

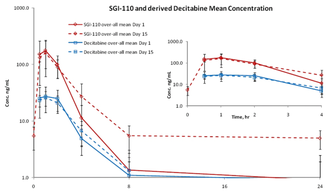
SGI-110 in Monkeys: Safety & PD

Species	Dosing schedule	Dose level/ # of animals	Tolerability	Hematology results	PD results
Monkey	Once/wk for 3 wks, 2 wks recovery	3 mg/kg 4 animals	No mortality, no clinical observations	Average neutrophil levels decreased and continued to decrease two weeks after the last dose; Other parameters were not affected in contrast with rat and rabbit models	Global DNA methylation significantly reduced up to day 29.

3 mg/kg/day in monkeys equivalent to 36 mg/m^2/day

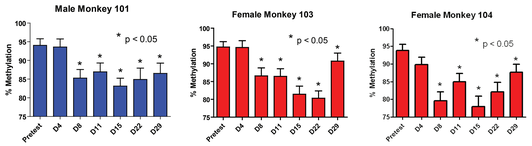
PK of SGI-110 and Decitabine: Monkey

SGI-110 Weekly, SQ



- SQ dose of 3 mg/kg SGI-110 on Days 1, 8 and 15
- SGI-110 levels an order of magnitude higher than those of decitabine
- Slower conversion to decitabine over 24 hr compared to rats and rabbits
- No significant accumulation observed for SGI-110 or decitabine

Monkey LINE-1 Methylation from SQ Dosing



- SQ dose of 3 mg/kg SGI-110 on Days 1, 8 and 15 in 4 animals (LINE-1 methylation could not be evaluated in 1 of the 4 animals)
- DNA from whole blood underwent bisulfite modification followed by pyrosequencing analysis
- Statistically significant decrease ($P<0.05$) in LINE-1 methylation observed in all evaluable animals up to Day 29
- Global hypomethylation was also observed in rats (data not shown)

Conclusions

- Safety data from SGI-110 in rat, rabbits, and monkey showed the expected myelosuppression which was reversible at the tolerated doses
- PK levels of SGI-110 and the derived decitabine increased with higher doses, SGI-110 converts rapidly to decitabine in rat and rabbit while the conversion in monkeys is slower probably contributing to more sustained efficacy
- Global LINE-1 hypomethylation was achieved in both rats and monkey at well tolerated doses
- Significant LINE-1 methylation reduction was sustained in monkeys for up to 4 weeks using the 3 weekly SQ injections (Days 1, 8, and 15) offering a less frequent and more convenient dosing regimen
- Clinical phase I/II is ongoing in refractory MDS or AML patients with both SQ daily x5 and weekly x3 every 28 days.
- Starting human dose is 3 mg/m^2/day, daily x5; and 6 mg/m^2/day, weekly x3.

52nd ASH Annual Meeting, Orlando FL, December 4-7, 2010

SGI110-PB(1003)