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Evaluation of Oral Bioavailability and Intermittent Dosing Schedules for Pharmacodynamic Effects by SGI-110, a Novel Subcutaneous (SQ) Second Generation Hypomethylating Agent (HMA), in Male Cynomolgus Monkeys

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Abstract

Abstract: Background: SGI-110 is a second generation hypomethylating agent consisting of a dinucleotide of decitabine and deoxyguanosine designed to release decitabine upon administration. SGI-110 is being evaluated in patients with relapsed/refractory MDS and AML, and also ovarian cancer (combination with carboplatin) and HCC. This study evaluated pharmacodynamic effects of three alternate weekly intermittent dosing schedules of Subcutaneous (SQ) SGI-110, and also the bioavailability of SGI-110 when given orally. In addition, a dose range-finding (DRF) study of 2-cycle duration was conducted in monkeys using three different regimens.

Methods: Group A received a single 10 mg/kg dose of SGI-110 by oral gavage. Group B received SQ injections of 1.5 mg/kg on Days 1,2, 8,9 and 15,16; Group C received SQ injections on Days 1,4, 8,11, 15 and 18; group D received injections on Days 1,2,3 and 15,16,17. Pharmacokinetics of SGI-110 and decitabine were evaluated on Day 1 for all treatment groups. The pharmacodynamic effect of SGI-110 was assessed through Day 28 (Days 1, 4, 8, 11, 14, 21 and 28) by measuring LINE1 methylation status in PBMCs from monkeys in groups B, C and D.

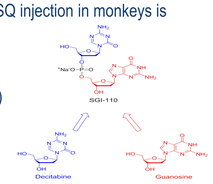
Results: Animals tolerated SGI-110 treatment well through the study. Relative oral bioavailability of decitabine appeared to be very low with only trace amounts of decitabine detected in plasma from Group A animals. A time-dependent LINE1 hypomethylating effect was observed in monkeys from Groups B, C and D relative to baseline pre-treatment values from Day 1. The maximal extent of hypomethylation varied between 11-14% within the groups and was achieved earlier in the cycle for Groups B and C (Day 11 and Day 14, respectively), whereas for Group D a second maximum peak effect was observed on Day 21. All groups trended towards baseline by Day 28 but Groups C and D still had significant hypomethylation (8-9%) present by the end of the study. On average, Group C and D seemed to achieve the maximum and most prolonged hypomethylation but only group C had a sustained effect.

The 2-cycle DRF study used three regimens: Daily X5, Daily X10 and Twice-Weekly for 3 weeks, at two different dose levels each, with total cycle dose for all regimens at 10.5 or 15 mg/kg/cycle. Hematology, PK for all doses, as well as PD for the twice-weekly regimen are presented here.

Conclusions: SGI-110 was well tolerated in cynomolgus monkeys for both single PO and repeat SQ dosing using intermittent alternate-weekly and daily X5 or X10 schedules. Oral bioavailability of SGI-110 was very low, suggesting very high first-pass contribution to SGI-110 and decitabine clearance upon oral administration. All SQ schedules achieved significant hypomethylating effect; the extent and the duration of effect were more favorable for Groups C and D with group C showing a more sustained effect over the 28-day cycle. We concluded that the twice-weekly SQ regimen is a highly effective and convenient regimen to study in clinical trials as it may achieve a more sustained pharmacodynamic effect.

Introduction

- SGI-110 is a 2nd generation hypomethylating agent and is being investigated in Phase 1 and 2 trials for hematological and solid tumor indications.
- SGI-110 is a pro-drug and upon subcutaneous (SQ) injection efficiently converts to decitabine by cleavage via phosphodiasterase (PDE) enzymes. The rate of conversion is species-dependent: very fast in rodents and much slower in primates. The pharmacokinetic profile of decitabine appearance after SQ injection in monkeys is predictive of profile observed in the clinic.
- SQ injection with SGI-110 results in longer decitabine exposure window compared to decitabine IV-infusion.
- SGI-110 is not a substrate for cytidine deaminase (CDA) which is responsible for inactivation of decitabine.
- Safety, tolerability, PK and PD in cynomolgus monkeys were evaluated for various dosing schedules of SGI-110.



Methods

Cynomolgus monkeys (Macaca fascicularis) were chosen for this study as a species that is commonly used for nonclinical toxicity evaluation of pharmaceuticals intended for clinical use. In addition, monkey is the species that is closest to humans with respect to the pharmacokinetic profile of SGI-110 and its active metabolite decitabine after SQ dosing.

Study 1. Dose formulations were prepared weekly by reconstituting the test article with the diluents. Test article vials contained 100 mg of SGI-110. These vials were reconstituted with 3 mL of the custom diluent to supply a concentration of 33.33 mg/mL. Prepared formulations were stored refrigerated when not in use and brought to room temperature prior to dosing. The animals were dosed according to the experimental design below and weighed for dose calculations on the day of dosing. Group A animals were dosed by oral gavage.

Dose Group	Day of Dosing	Route of Administration	Dose Level (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	Number of Animals
A	1	PO	10	33.33	0.300	3
B	1, 2, 8, 9, 15, 16	SQ	1.5	33.33	0.045	3
C	1, 4, 8, 11, 15, 18	SQ	1.5	33.33	0.045	3
D	1, 2, 3, 15, 16, 17	SQ	1.5	33.33	0.045	3

Following dosing, pharmacokinetic blood samples were collected via venipuncture pre-dose and at 0.25, 0.5, 1, 1.5, 2, 4, and 6 hours post-dose on Day 1 and processed to plasma. Collected plasma samples were analyzed to determine concentrations of SGI-110 and decitabine.

Pharmacodynamic blood samples were collected from animals in Groups 2-4, via venipuncture pre-dose on Day 1 and on Days 4, 8, 11, 14, 21, and 28.

LINE1 methylation was evaluated in bisulfite-treated DNA by pyrosequencing.

Study 2 (DRF)

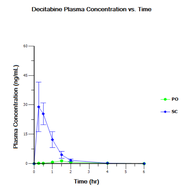
Dose Group	Day of Dosing Cycles 1 and 2	Dose (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)
1	1 – 5	2.1	33.33	0.063
2	1 – 5	3	33.33	0.09
3	1 – 5 and 8 – 12	1.05	33.33	0.032
4	1 – 5 and 8 – 12	1.5	33.33	0.045
5	1, 4; 8, 11, 15, 18	1.75	33.33	0.053
6	1, 4; 8, 11, 15, 18	2.5	33.33	0.075

N=3 for all treatment groups

The animals were dosed SQ according to the experimental design presented in the table above. There were two dosing cycles 30 days apart.

Pharmacokinetics from Study 1

Relative oral bioavailability of decitabine (vs. SQ) was very low (1.3%)

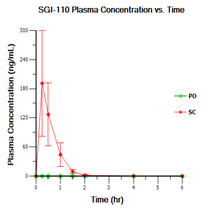


Summary of PK Parameters for Decitabine after Dosing with SGI-110

Dose (mg/kg)	N		$T_{½}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	AUC_{last} (ng*hr/mL)
10 (PO)	3	Mean	NA	1.67	1.44	2.33
		SD	NA	0.29	0.69	0.89
1.5 (SQ)	9	Mean	0.60	0.39	30.63	27.51
		SD	0.08	0.13	11.96	4.56

*Groups B, C and De were analyzed together as they received the same SQ dose of 1.5 mg/kg

Relative oral bioavailability of SGI-110 vs. SQ was zero

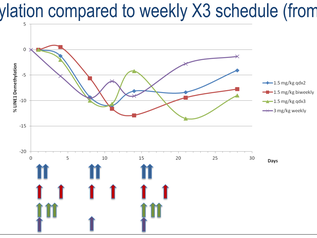


Summary of PK Parameters for Decitabine after SGI-110 Dose

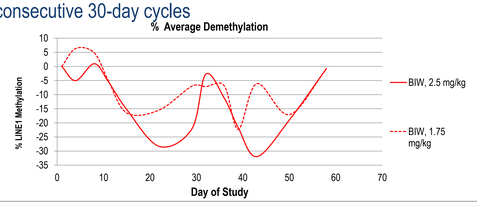
Dose (mg/kg)	N		$T_{½}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	AUC_{last} (ng*hr/mL)
10	3	Mean	NA	N/A	0	0
		SD	NA	N/A	0	0
1.5	9	Mean	0.45	0.25	191.07	125.27
		SD	0.11	0.00	108.55	43.10

*Groups B, C and D were analyzed together as they received the same SQ dose of 1.5 mg/kg

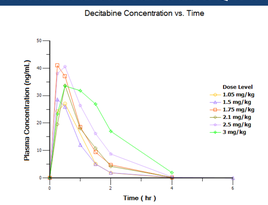
SGI-110 administered twice-weekly for 3 weeks improves the extent and duration of LINE1 demethylation compared to weekly X3 schedule (from a previous study).



The extent and duration of LINE1 demethylation after the twice-weekly for 3 weeks dosing schedule is dose-dependent. Both dose levels were well tolerated for 2 consecutive 30-day cycles



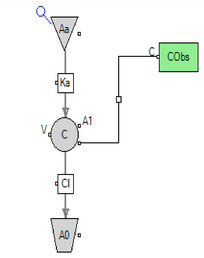
PK Profile of Decitabine after various SQ Doses of SGI-110

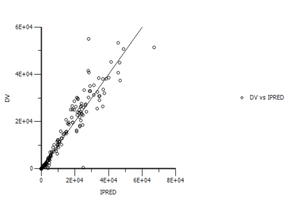


Summary of PK Parameters for Decitabine

Dose (mg/kg)		C_{max} (ng/mL)	T_{max} (hr)	Auc_{last} (ng*hr/mL)	CL/F (L/hr/kg)	$T_{½}$ (hr)
1.05	**Mean**	**27.1**	**0.5**	**29.3**	**35.8**	**0.4**
	SD	2.7	0.0	0.0	0.03	0.0
1.50	**Mean**	**30.5**	**0.4**	**28.0**	**55.4**	**0.6**
	SD	10.3	0.1	5.8	12.5	0.1
1.75	**Mean**	**41.7**	**0.3**	**44.3**	**41.1**	**0.4**
	SD	9.3	0.1	11.3	10.3	0.0
2.10	**Mean**	**33.7**	**0.5**	**37.5**	**63.8**	**0.4**
	SD	4.3	0.0	15.0	30.7	0.0
2.50	**Mean**	**42.3**	**0.6**	**57.3**	**45.5**	**0.4**
	SD	9.7	0.4	15.5	11.1	0.1
3.00	**Mean**	**35.8**	**0.8**	**71.8**	**48.9**	**0.6**
	SD	14.5	0.7	22.0	20.0	0.1

Pharmacokinetic Model for Decitabine

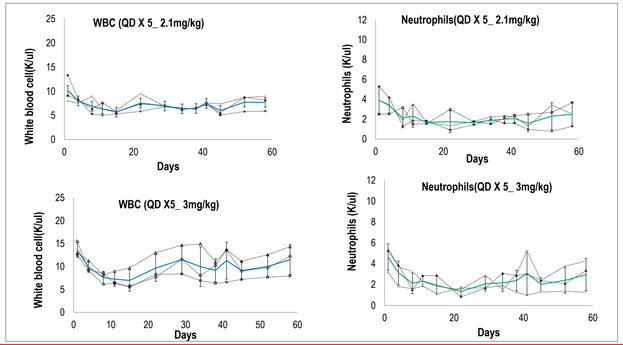




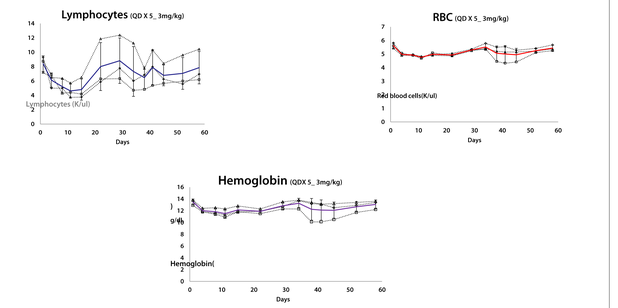
A 1-compartment model was developed with first-order absorption and elimination that fit the data well. A multiplicative residual error model was used. Data from 27 animals dosed SQ were utilized to fit the model.

Two-Cycle Dose Range-Finding Study in Monkeys: Key Hematological Changes after 3 Different SQ Dosing Regimens with SGI-110

Daily x5

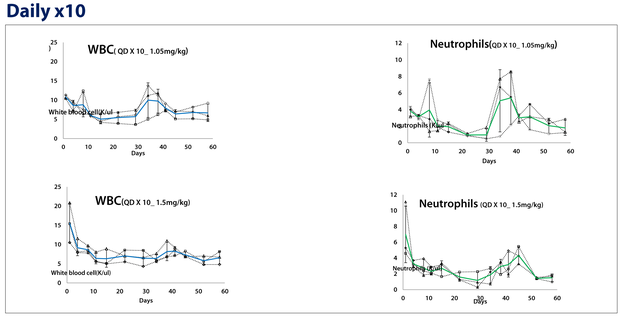


Daily x5

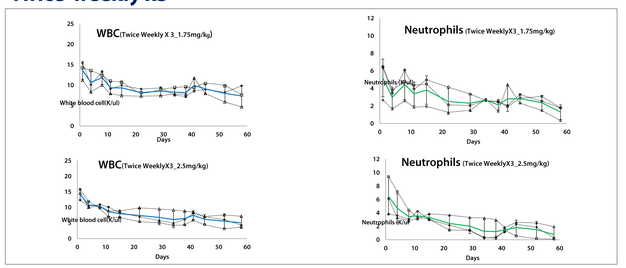


No sustained effects on Lymphocytes, RBCs or Hemoglobin

Daily x10



Twice-weekly x3



Conclusions

- All intermittent dosing schedules of subcutaneous injections with SGI-110 were tolerated well in cynomolgus monkeys. Hematological changes (neutropenia and leukopenia) were sustained over two cycles of dosing. However, there were no cumulative hematological changes in the 2nd cycle.
- Relative to SQ, SGI-110 is not orally bioavailable while %F for decitabine after SGI-110 SQ injection was very low (1.3%).
- PD analysis, as measured by LINE 1 demethylation, suggests intermittent alternate weekly dosing schedules may achieve longer duration and persistent hypomethylation effect.
- The twice-weekly for 3 weeks dosing schedule was tolerated at 2.5 mg/kg/dose. The extent of demethylation was further improved compared to that observed at lower doses and the effect was maintained for the 2nd cycle of dosing.
- Alternate intermittent dosing schedule of BIW X3 may be considered for clinical evaluation for additional indications.

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Poster can be downloaded from www.astx.com

SGI-110-PB(1302)