Abst. No. 2321

SGI-110 SQ Provides Superior Disposition Profile for Active Metabolite Decitabine than Decitabine IV Infusion: Results from Mass Balance and Tissue Distribution Study in Cynomolgus Monkeys and In Vitro Human Studies

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BACKGROUND

- SGI-110 is a 2nd generation hypomethylating agent. It is a dinucleotide of decitabine (DAC) and deoxyguanosine; is resistant to deamination by cytidine deaminase and is in clinical development for hematologic malignancies and solid tumors
- Clinical PK data for SGI-110 show lasting exposures (8 hr+) in parent form
- Due to the slow release from SGI-110 after SQ injection, exposure window for the active metabolite decitabine is prolonged compared to IV DAC, which is the proposed basis for the improved clinical activity emerging from early clinical trials with SGI-110
- The objective of this study was to characterize the mass balance and tissue distribution of [^{14}C]SGI-110 compared to IV [^{14}C]DAC and evaluate the potential uptake into cells of SGI-110 in parent form prior to conversion to active metabolite DAC

METHODS

- The mass balance (MB) of administered radioactivity was evaluated in cynomolgus monkeys (n=4, 1 per time-point) following a single SQ dose of [^{14}C]SGI-110 or a single molar equivalent IV 1-hr infusion of [^{14}C]decitabine. Tissue distribution of the radiolabel was evaluated using quantitative whole-body autoradiography (QWBA) up to 24 hours following dosing (1, 2, 6 and 24-hr).
- The position of the radiolabel was within the DAC structure of SGI-110 and the same as on DAC. Study was designed with clinically relevant dose levels.
- SGI-110 was evaluated as a substrate in human uptake transporter panel in MDCK-II cells.
- Uptake into cells was also assessed by LCMS/MS in incubation of SGI-110 with fresh human whole blood.

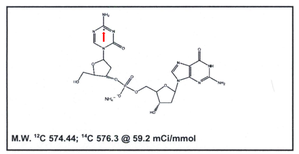


Figure 1: Position of the radiolabel (*) in SGI-110 was within decitabine structure

Table 1: Group Assignment and Dose Levels

Dose Group	Test Article	Route of Administration	Dose Level (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	Number of Animals
1	[^{14}C]SGI-110	SQ	5.1	26.26	0.20	4
2	[^{14}C]Decitabine	IV Infusion (1 hour at 1.5 mL/kg/hr)	2	1.33	1.5	4

RESULTS

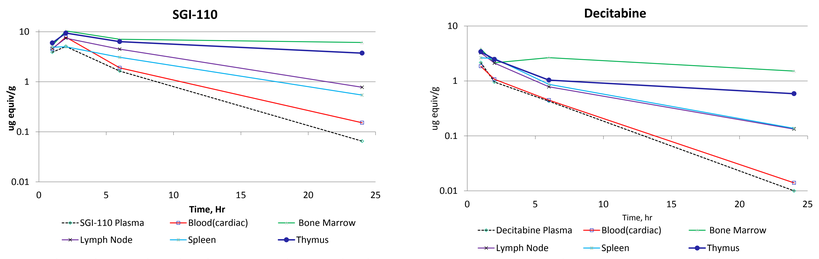
SGI-110 Mass Balance

Table 2: Recovery of the Administered Dose for [^{14}C]SGI-110

Sample	% of Administered Dose
Urine	56.4
Cage Wash	48.2
Feces	3.3
Total	**107.8**

- Majority of radioactivity in administered dose was recovered in urine and cage wash (presumed urinary origin), suggesting that excretion is mostly renal

Figure 2: Tissue Distribution: Vascular, Lymphatic/Plasma – 24-hrs



More decitabine-related radioactivity detected in bone marrow and all vascular compartments after equimolar SGI-110 SQ administration compared to IV decitabine.

Tissue Distribution by QWBA

Table 3: Tissues with the highest exposures of [14C]-derived radioactivity

Tissue	Radioactivity AUC$_t$ (µM equiv*hr)	
	SGI-110	Decitabine
Bone Marrow	**284.42**	**227.94**
Kidney Cortex	259.22	198.58
Large Intestine	239.81	124.55
Thymus	230.67	115.04
Urinary Bladder	216.14	>ULOQ*
Kidney Medulla	204.82	155.46
Stomach (gastric mucosa)	165.78	97.75
Liver	155.77	78.61
Pituitary Gland	141.55	104.07
Prostate	131.75	108.92

* Not calculated due to some values above the upper limit of quantitation

Table 4: Tissues with the lowest exposures of [^{14}C]-derived radioactivity

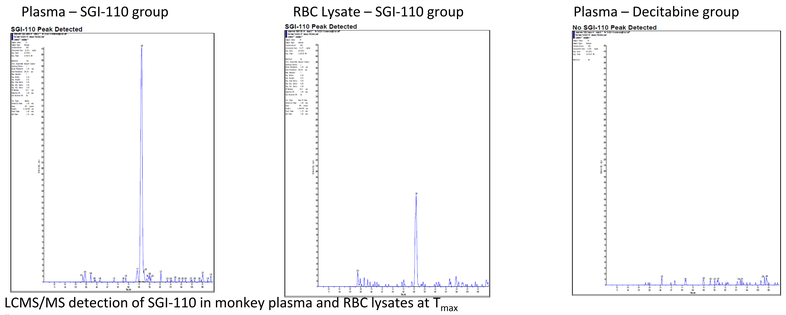
Tissue	Radioactivity AUC$_t$ (µM equiv*hr)	
	SGI-110	Decitabine
Brain (cerebrum)	10.87	11.92
Brain (cerebellum)	10.72	10.23
Eye (lens)	9.90	6.18
Bone	8.36	2.23
Spinal Cord	8.16	6.31
Brain (medulla)	7.60	6.90
Cerebrospinal Fluid	4.27	3.46

Table 5: Decitabine-related radioactivity in blood fractions and bone marrow

Tissue	Radioactivity AUC$_t$ (µM equiv*hr)	
	SGI-110	Decitabine
Plasma	61.08	40.72
Blood	57.44	41.59
RBC	53.79	40.28
Buffy Coat	64.55	54.73
Bone Marrow	284.22	227.54

More decitabine-related radioactivity AUC exposures in blood fractions and bone marrow after equimolar SGI-110 SQ than IV decitabine.

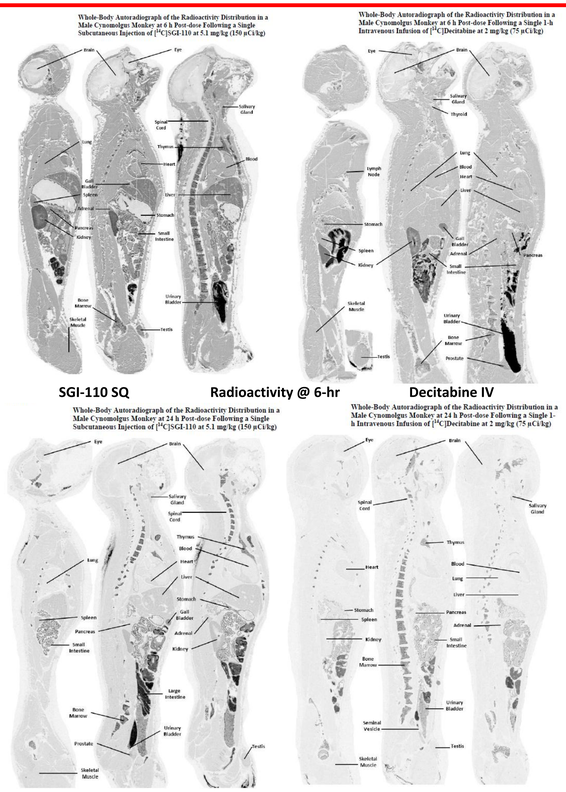
Figure 3: SGI-110 Peak Detected in Monkey Plasma and Intracellularly in RBC lysate#



LCMS/MS detection of SGI-110 in monkey plasma and RBC lysates at T_{max}

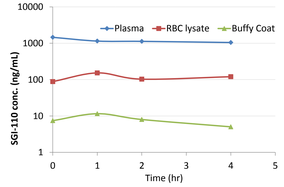
RBC lysates were used as a proxy for intracellular measurement for SGI-110 due to sample availability and established methodology

Figure 4: Tissue Distribution in Monkey: QWBA



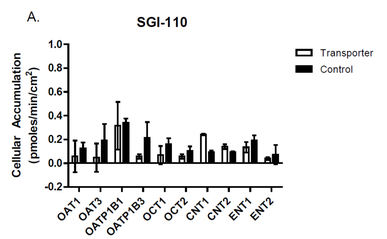
- Higher Levels of radioactivity present in key tissues when dosed with equimolar SQ SGI-110 than IV decitabine

Figure 6: SGI-110 Incubation (2 µM) in Fresh Human Whole Blood



- SGI-110 detected in intracellular compartment in both RBC and buffy coat lysates (levels in buffy coat underestimated due to additional dilution required for separation and extraction). Intracellular presence likely due to equilibration rather than active uptake.

Figure 5: Evaluation of SGI-110 as a substrate in a panel of human transporters



- SGI-110 is a possible substrate for CNT1 and CNT2, but not of ENT1 or ENT2

SUMMARY

- Consistently higher decitabine-related radioactivity exposures were detected in most tissue compartments with SGI-110 compared to decitabine.
- SQ SGI-110 appears to deliver active metabolite decitabine to key tissues, including bone marrow, more efficiently than equimolar dose infusion of IV decitabine due to its presence in parent form in circulation over a relatively extended time and protracted release of decitabine.
- Mass balance data indicate excretion mainly through the renal/urinary route.
- SGI-110 was detected in intracellular compartment and may also be a substrate for CNT1 and CNT2 transporters.

Poster presented at: AACR Annual Meeting, San Diego, CA April 5 – 9, 2014

Poster can be downloaded from www.astx.com