**BACKGROUND**

- SGI-110 is a 2nd generation hypomethylating agent. It is a dinucleoside of decitabine (DAC) and deoxoguanosine; 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 h) 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 [14C]SGI-110 compared to IV [14C]decitabine and evaluate the potential uptake into cells of SGI-110 in parent form prior to conversion to active 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 [14C]SGI-110 or a single molar equivalent IV 1-hr infusion of [14C]decitabine. Blood samples were collected for 120 h post-dose. Plasma and 10 key tissues were evaluated by LCMS/MS in incubation of SGI-110 with fresh human whole blood.

**RESULTS**

- **SGI-110 Mass Balance**
  - Table 2: Recovery of the Administered Dose for [14C]SGI-110
  - Majority of radioactivity in administered dose was recovered in urine and cage wash (presumed urinary origin), suggesting that excretion is mostly renal.

- **Table 1: Group Assignment and Dose Levels**
  - Dose Group Table Article Route of Administration Dose Level (mg/kg) Dose Concentration (mg/mL) Dose Volume (mL/kg) Number of Animals
  - 1 [14C]SGI-110 IV Infusion 5.1 26.26 0.20 4
  - 2 Decitabine (1 hour at 1.5 mg/kg) 2 1.33 1.5

- **Figure 1: Position of the radiolabeled [14C]SGI-110 within dectasite structure**

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

- **Tissue Distribution by QWBA**
  - Table 3: Tissues with the highest exposures of [14C]-derived radioactivity
    - Tissue Radioactivity AUC, (µM equiv/hr)
    - Bone Marrow 284.42 227.94
    - Kidney Cortex 250.22 198.38
    - Large intestine 238.81 124.55
    - Thymus 230.67 115.04
    - Urinary Bladder 216.14 **SMLO**
    - Kidney Medulla 204.82 155.46
    - Stomach (gastric mucosa) 165.78 97.75
    - Liver 155.77 78.61
    - Pituitary Gland 141.55 104.67
    - Prostate 131.75 108.92

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

- **Figure 3: SGI-110 Peak Detected in Monkey Plasma and Intracellularly in RBC lysates**

- **Table 4: Tissues with the lowest exposures of [14C]-derived radioactivity**
  - Tissue Radioactivity AUC, (µM equiv/hr)
  - 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

- **Figure 4: Tissue Distribution in Monkey: QWBA**

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

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

**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 prolonged 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 ENT1 and CNT2 transporters.

---

**Poster presented at: AACR Annual Meeting, San Diego, CA April 5 – 9, 2014 © Astex Pharmaceuticals, Inc.**

**Poster can be downloaded from www.astx.com**