Abstract (Updated October 2007)

Purpose: To describe the pharmacokinetic properties of SNS-595 observed in phase 1 solid and hematologic malignancy trials. SNS-595 is a replication-dependent DNA-damaging agent that causes irreparable DNA double-strand breaks in cancer cell nuclei via cleavage of DNA at sites of replication origin, resulting in cell death.

Methods: In recent phase 1 studies, SNS-595 was dosed at escalating doses to patients (pts) with advanced solid cancers as an IV infusion over 10 minutes on a 3-weekly (q3w) or 5-day (q5d) schedule, respectively. In study SPO-0001, SNS-595 was administered to pts with advanced or refractory acute leukemias as an IV infusion over 10 minutes on a q3w (arm A) or q5d (arm B) schedule. Pharmacokinetic (PK) analyses were performed in all studies.

Results: PK samples collected across all phase 1 studies (SPO-0001 and SPO-0002) were analyzed using validated LC-MS/MS methods. PK parameters were obtained in 40 pts receiving doses ranging from 5 to 100 mg/m².

Background

SNS-595 is a replication-dependent DNA-damaging agent that causes irreversible growth arrest of proliferating cells and rapid apoptosis resulting from cell cycle arrest and DNA fragmentation. SNS-595 is an active topoisomerase II inhibitor that includes DNA intercalation, as well as a unique inhibition of topoisomerase II that causes irreversible DNA damage. In vivo, SNS-595 has demonstrated single agent activity in 2nd line lung cancer (NSCLC + SCLC) and platinum-resistant ovarian cancer. In non-critical species SNS-595 has demonstrated favorable pharmacokinetics properties with tight inter-individual variability, low protein binding, linear terminal pharmacokinetics, and lack of enterohepatic recycling. Direct intracellular cleavage (25%), direct intracellular recycling (2%), and urinary excretion (73%) were major metabolic pathways. In rats, SNS-595 was unchanged, with no phase 1 metabolites, and conjugated with glucuronic acid.

SNS-595 PK Parameters Are Unchanged After Repeat Administration

Solid lines represent the mean value, boxes represent one standard deviation, and whiskers represent the full range. The p-values are derived from Wilcoxon Signed Rank tests, evaluating whether the serial changes from day 1 to day 11 remained J-

Summary & Conclusions

Summary:

- SNS-595 is well-tolerated with single iv administration.
- Dose escalation resulted in a linear increase in exposure.
- Repeat administration caused a statistically significant decrease in volume of distribution (Vss) and clearance (CL) with a median of 12% (5%) and 25% (12%), respectively. Significant reductions in Vss and CL were observed following repeat administration.
- On day 11, AUC/Dose and CL were similar to day 1, indicating no change in the pharmacokinetics of SNS-595 after a single dose.
- AUC/Dose values are an aggregate measure of the total exposure to SNS-595 and are calculated as the area under the plasma concentration-time curve divided by the dose.
- Vss is an estimate of the volume of distribution of SNS-595 in the body and is used to estimate the distribution of the drug in tissues and fluids.
- CL is the rate at which SNS-595 is cleared from the body and is used to estimate the rate at which the drug is removed from the body.
- Tmax is the time at which the maximum concentration of SNS-595 is observed in the plasma.
- Cmax is the maximum concentration of SNS-595 observed in the plasma.
- The p-values are derived from Wilcoxon Signed Rank tests, evaluating whether the serial changes from day 1 to day 11 remained statistically significant.

Conclusions:

- The consistent and predictable PK properties allow for selection of doses that optimize pharmacological and minimize toxicological effects, facilitating the ongoing development of SNS-595 in acute leukemias and platinum-resistant ovarian cancer.