

SNS-595 Demonstrates Predictable, Dose-Proportional Pharmacokinetics In Three Phase 1 Clinical Trials



SUNESIS

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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 irreversible G2 arrest and a rapid onset of apoptosis. A secondary mechanism for SNS-595 is a unique inhibition of topoisomerase II that causes highly selective DNA damage.

Methods: In studies SPO-0001 and SPO-0002, SNS-595 was administered to patients (pts) with advanced solid cancers as an IV infusion over 10 minutes on a q3w and qw x3 schedule, respectively. In study SPO-0004, SNS-595 was administered to pts with advanced or refractory acute leukemias as an IV infusion over 10 minutes on a qw x3 (arm A) or biw x2 (arm B) schedule. Pharmacokinetic (PK) analyses for SNS-595 were performed on plasma samples collected during cycle 1, day 1 administration (SPO-0001 and SPO-0004 arm A), days 1 and 14 post-administration (SPO-0002), and days 1, 4, 8, and 11 post-administration (SPO-0004 arm B). SNS-595 was analyzed using a validated LC-MS/MS method, and PK parameters were estimated using noncompartmental analysis.

Results: Pharmacokinetic properties were analyzed in 40 pts receiving doses of 3-75 mg/m² in SPO-0001, 20 pts receiving doses of 3-24 mg/m² in SPO-0002, 33 pts receiving doses of 18-90 mg/m² in SPO-0004 arm A, and 29 pts receiving doses of 9-50 mg/m² in SPO-0004 arm B. Across all studies and dose levels, drug exposure as measured by AUC is similar in the various patient populations and increases linearly with dose (ranging between 1-60 µg·hr/mL). CL, V_{ss}, and T_{1/2} estimates remain constant with increasing doses and average 2 L/hr/m², 50 L/m², and 20 hrs, respectively. PK properties do not change with repeat weekly or biweekly administrations, indicating a lack of accumulation upon repeat administration of SNS-595.

Conclusions: SNS-595 has demonstrated excellent pharmacokinetic properties in three phase 1 studies. There is a proportional increase in exposure with dose, low inter- and intra-patient variability and no evidence of accumulation of drug following repeat administration across the schedules used. The consistent and hence predictable PK properties combined with the safety profile observed in the phase 1 studies will facilitate development of SNS-595.

Background

SNS-595 is a replication-dependent DNA damaging agent that causes irreversible growth arrest of proliferating cells and rapid apoptosis resulting in potent anti-tumor activity. SNS-595 has a mechanism of action that includes DNA intercalation, as well as a unique inhibition of topoisomerase II that causes highly selective DNA damage. In the clinic, SNS-595 has demonstrated single agent activity in 2nd line lung cancer (NSCLC + SCLC) and platinum-resistant ovarian cancer. In non-clinical species SNS-595 has demonstrated favorable pharmacokinetics properties with tight inter-individual variability, low-medium clearance, long terminal half-lives, and dose-linear increase in exposures. Routes of elimination in rats included biliary excretion (~40%), direct intestinal secretion (~30%), and urinary excretion (~20%). In rats, SNS-595 was excreted unchanged, as phase 1 metabolites, and conjugated with glucuronic acid.

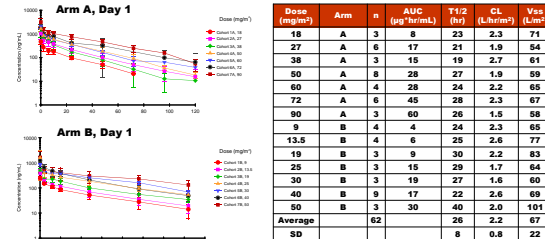
Methods

SPO-0001 - Drug administered by IV bolus to patients with solid tumors, once every three weeks with a starting dose of 3 mg/m². **SPO-0002** - Drug administered by IV bolus to patients with solid tumors, weekly x 3 followed by 14 days of observation with a starting dose of 3 mg/m². **SPO-0004** - Drug administered by IV bolus to patients with hematologic tumors, weekly x 3 with a starting dose of 9 mg/m² (arm A) and twice-weekly on days 1, 4, 8, 11 (arm B) with a starting dose of 18 mg/m². Dose escalation was performed in cohorts of 3 patients and doses were doubled until the first Grade 2, related AE or abnormal lab value was observed. Subsequent dose escalations followed a modified Fibonacci scheme. Pharmacokinetic (PK) analyses for SNS-595 were performed on plasma samples collected during cycle 1, day 1 administration (SPO-0001 and SPO-0004 arm A), days 1 and 14 post-administration (SPO-0002), and days 1, 4, 8, and 11 post-administration (SPO-0004 arm B). SNS-595 was analyzed using a validated LC-MS/MS method with a lower limit of quantitation of 1 ng/mL.

PK parameters were estimated using noncompartmental analysis. For assessment of linearity, individual PK parameters were plotted against the administered dose. A linear regression analysis was performed to assess whether the regression line deviated from 0. To assess serial changes after repeat administration, the within-patient differences in pharmacokinetic parameters between Days 4 & 1, 8 & 1, 11 & 1 were computed and subjected to Wilcoxon Signed Rank tests.

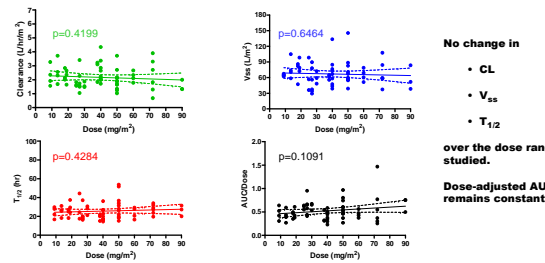
SPO-0004: Acute Leukemias, Qw x 3 or BiW x 2

Concentration-Time-Profiles



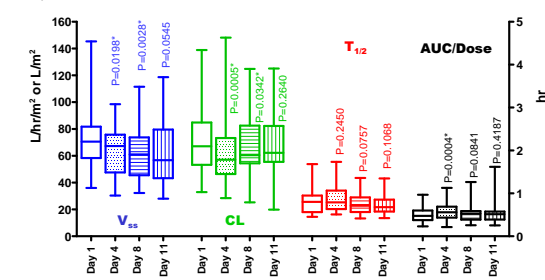
SNS-595 Exposure Increases Dose-linearly

Solid lines represent the linear regression based on mean values. Dotted lines represent 95% confidence interval. A p-value of < 0.05 would indicate that the slope of the regression line differs significantly from zero.



Repeat Administration of SNS-595 Results in Small Changes in PK Parameters

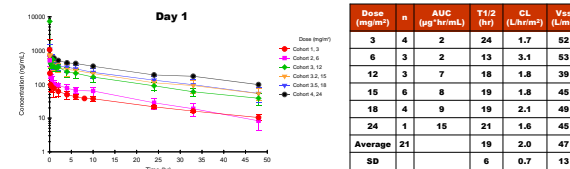
Solid lines represent the mean value, boxes represent one standard deviation, and whiskers represent the range. The p-values are derived from Wilcoxon Signed Rank tests, evaluating whether the serial changes from Day 1 differ from zero.



Repeat administration caused a statistically significant decrease in volume of distribution and clearance on Days 4 and 8 by a median of 12 and 0.28 value units. Statistical significance was not observed on Day 11. T_{1/2} remained constant. AUC/Dose increased by a median of 0.09 value units on Day 4, but remained unchanged on Days 8 and 11.

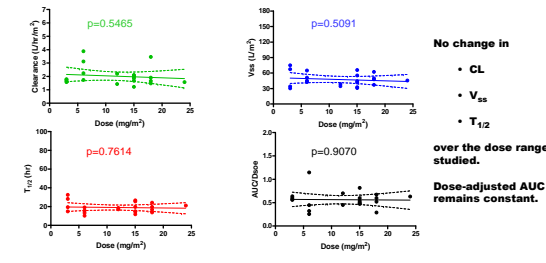
SPO-0002: Solid Tumors, Qw x 3

Concentration-Time-Profiles



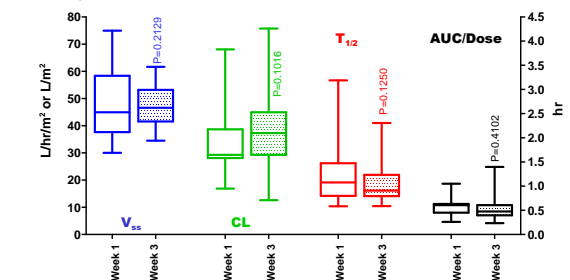
SNS-595 Exposure Increases Dose-linearly

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SNS-595 PK Parameters Are Unchanged After Repeat Administration

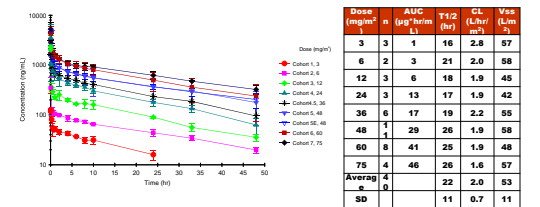
Solid lines represent the mean value, boxes represent one standard deviation, and whiskers represent the range. The p-values are derived from Wilcoxon Signed Rank tests, evaluating whether the serial changes from Day 1 differ from zero.



Repeat administration caused no statistically significant change in any of the PK parameters.

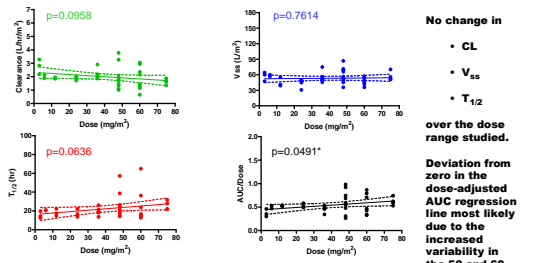
SPO-0001: Solid Tumors, Q3w x3

Concentration-Time-Profiles



SNS-595 Exposure Increases Dose-linearly

Solid lines represent the linear regression based on mean values. Dotted lines represent 95% confidence interval. A p-value of < 0.05 would indicate that the slope of the regression line differs significantly from zero.



Summary & Conclusions

Summary:

SNS-595 shows reproducible pharmacokinetics in three studies in patients with solid and hematologic tumors.

SNS-595 exposures increase dose-linearly; clearance, volume of distribution and half-life remained unchanged over the dose range.

SNS-595 plasma concentrations show biphasic decline, with a clearance of 2 L/hr/m², a volume of distribution of 50 L/m², and a half life of 20 hr.

SNS-595 pharmacokinetics remain unchanged after repeat administration in solid tumor patients. V_{ss} and CL show a small, transient change in patients with hematologic malignancies upon repeat administration, which is likely not pharmacologically important.

Conclusions:

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