

# Nonclinical pharmacokinetics, distribution, and excretion of SNS-314, a novel, selective Aurora kinase inhibitor

Marc J. Evanchik, Ute Hoch, Tarra Fuchs-Knotts, Jeffrey A. Silverman  
Sunesis Pharmaceuticals Inc., South San Francisco, CA, USA

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## ABSTRACT

**Background:** The Aurora kinase family is comprised of three proteins, Auroras A, B and C that function as key regulators of cell progression through mitosis and cytokinesis and may be important targets in anti-cancer therapy. SNS-314 is a novel small molecule that potentially inhibits all three Aurora proteins in the low-nanomolar range. SNS-314 has robust anti-tumor activity in a wide range of human xenograft tumor models in mice using an intermittent dosing schedule. SNS-314 is currently being investigated in a phase 1 trial to evaluate its safety and pharmacokinetic properties in humans.

**Results:** Pharmacokinetic studies were conducted in mice, rats and dogs after single and repeated administration. In rising dose pharmacokinetic studies, SNS-314 displays non-linear systemic exposure; the area under the concentration curve increases more than dose linearly. This is most pronounced in rats and mice and occurs to a lesser extent in dogs. Gender-related differences in pharmacokinetic parameters are observed in rodents and to a much lesser extent in dogs. Female rats had 1.3 to 2 fold greater plasma AUC than male rats. SNS-314 is rapidly and extensively distributed in both mice and rats when dosed IV, IP, or PO. Administration at 170 mg/kg to tumor bearing mice shows drug levels persisting in the tumor for more than 96 hours post-dose ( $T_{1/2} = 7.5$  hr), even though plasma levels were not measurable beyond 40 hours post-dose ( $T_{1/2} = 4.7$  hr). Whole-body autoradiography indicates [ $^{14}$ C]SNS-314 related radioactivity is widely distributed in tissues after an IV bolus dose with maximum concentrations observed 1 hour post dose. Approximately 70% of SNS-314 is eliminated through biliary excretion 48 hours post dose.

**Conclusion:** The favorable pharmacokinetic properties of SNS-314 including elevated tumor over plasma drug levels support clinical investigation of this oncology agent.

## METHODS

**Pharmacokinetic studies:** Pharmacokinetic parameters were estimated using noncompartmental analysis within WinNonlin v. 4.1. Quantification of SNS-314 was done by HPLC-MS/MS on SNS-314 after extraction from plasma and urine. CD-1 mice, Sprague-Dawley rats, and beagle dogs were administered a single bolus intravenous injection of SNS-314 and blood sampled (terminal bleed, mouse, rat (exposure and gender data), n=3; serial bleed, rat and dog) between 5 min - 24 hours. Bioavailability profile in mice was determined after administration of 50 mg/kg IV, IP, and PO with blood sampling 15 min - 16 hr post administration.

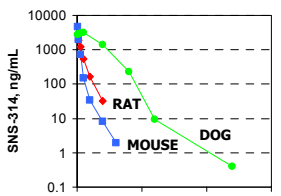
**Mass balance and elimination of SNS-314:** [ $^{14}$ C]SNS-314 was administered as a IV bolus dose of 50 mg/kg to male rats. Rats were femoral vein and bile duct cannulated to allow for the evaluation of the rate and extent of elimination of total radioactivity from urine, bile, and feces. Total radioactivity was analyzed by liquid scintillation counting. Samples were also subject to HPLC-radiometric detection to elucidate the metabolic and elimination profile of SNS-314.

**Distribution studies:** Skin: Female nu/nu athymic mice were administered 170 mg/kg SNS-314 IP with terminal plasma and skin collections between 15 min - 16 hr post administration. Tumor: Female nu/nu athymic mice received HCT-116 colorectal cancer cell suspension (1:1 DPBS with cells:Matrigel) as a subcutaneous injection in the right hind flank. When tumors reached an average volume of 500 mm<sup>3</sup>, mice were sorted into groups of 3 per time point. Mice were administered 170 mg/kg SNS-314 IP and terminal blood and tumor samples were harvested between 15 min and 96 hours. SNS-314 was extracted from tumor after homogenization with 10 x w/v PBS. Quantification of SNS-314 was done by LC-MS/MS after extraction from plasma and tumor homogenate with acetonitrile. Half life estimates were made using the last 5 time points in tumor and last 3 time points in plasma.

**Protein binding studies:** Studies were performed using the Rapid Equilibrium Dialysis (RED) device (Linden Bioscience). Inserts were soaked in water for 10 min X 2, then removed and drained immediately prior to use. Inserts were placed into a Teflon base plate prior to the addition of spiked matrix (SNS-314 in plasma at 15  $\mu$ M) and buffer. All experiments were performed in duplicate and each chamber was sampled in duplicate. The samples were incubated for 4-6 h at 37 °C in a rotating incubator (100 rpm). SNS-314 was quantified using LC-MS/MS. Data from duplicate samples were sampled twice.

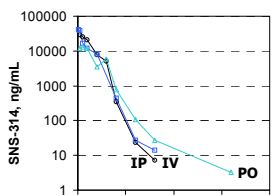
## PHARMACOKINETICS

### IV pharmacokinetics in mouse, rat, and dog



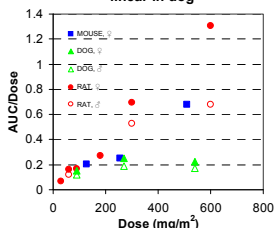
	MOUSE	RAT	DOG
Dose (mg/kg)	5	5	5
Dose (mg/m <sup>2</sup> )	15	30	90
C <sub>0</sub> ( $\mu$ g/mL)	7.1	3.6	2.8
AUC <sub>0-24</sub> ( $\mu$ g $\cdot$ hr/mL)	1.8	2.1	12.3
CL (mL/min/kg)	47.6	41.2	6.8
V <sub>d</sub> (L/kg)	1.0	1.8	1.0
T <sub>1/2</sub> (hr)	1.4	0.8	1.1

### SNS-314 is rapidly absorbed following IP or PO administration in mice

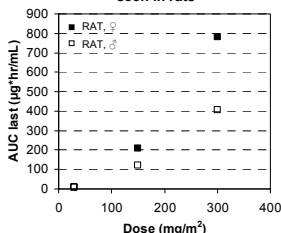


	IV	IP	PO
Dose (mg/kg)	50	50	50
C <sub>0</sub> ( $\mu$ g/mL)	42.0	-	-
AUC <sub>0-24</sub> ( $\mu$ g $\cdot$ hr/mL)	43.6	46.2	28.3
CL (mL/min/kg)	19.1	-	-
V <sub>d</sub> (L/kg)	1.2	-	-
T <sub>1/2</sub> (hr)	0.8	0.7	3.3
F (%)	-	106	65

### Exposure increase greater than increment in rodents but linear in dog



### Sex dependent exposure seen in rats

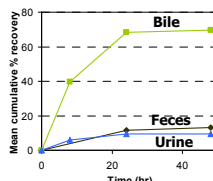


### Rat non-linear PK is due to changes in clearance

	60	300	600
Dose (mg/m <sup>2</sup> )			
CL (mL/min/kg)	17.2	4.0	2.0
V <sub>d</sub> (L/kg)	1.3	1.1	1.1
T <sub>1/2</sub> (hr)	1.4	1.7	5.9

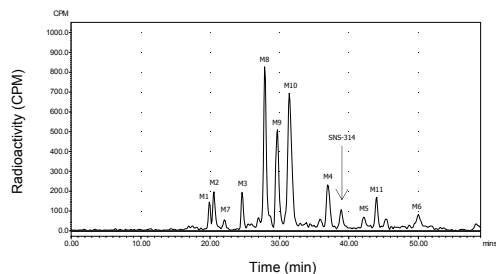
## ELIMINATION

### SNS-314 is predominately eliminated in bile

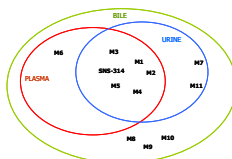


	Interval (hr)	Mean cumulative % recovery
Feces	0-24	11.8
	24-48	13.2
Bile	0-8	39.7
	8-24	68.5
	24-48	69.5
Urine	0-8	6.1
	8-24	9.4
	24-48	9.6
<b>Cumulative Total</b>	<b>24</b>	<b>89.7</b>
	<b>48</b>	<b>92.3</b>

### Majority of SNS-314 is eliminated as metabolized drug in rats

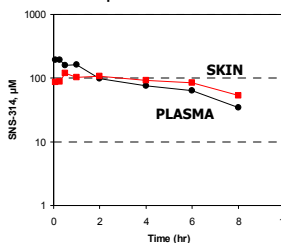


### Circulating and elimination pathway in rats

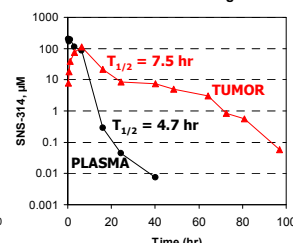


## DISTRIBUTION

### Plasma and skin PK profiles are similar



### Drug levels persist in HCT-116 tumor xenografts



### SNS-314 is highly protein bound

15 $\mu$ M SNS-314	Mean % bound
MOUSE	
RAT	$\geq 99.9$
DOG	
HUMAN	

## SUMMARY

- ✓ SNS-314 is absorbed rapidly and shows good oral bioavailability in rats
- ✓ SNS-314 is retained in tumors relative to the plasma compartment
- ✓ Main route of elimination is biliary excretion

## CONCLUSIONS

- ✓ PK profile in skin is similar to plasma allowing PD readouts in the skin to be directly correlated with drug concentrations measured in the plasma
- ✓ SNS-314 is being evaluated in a Phase 1 trial to evaluate its safety and tolerability in patients with solid tumors