

# A Phase 1 Trial of SNS-314, a Novel and Selective Pan-Aurora Kinase Inhibitor, in Advanced Solid Tumor Patients

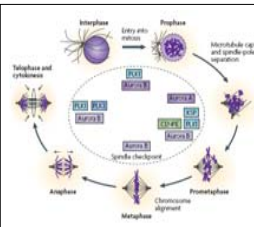
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## ABSTRACT - UPDATED

**Background:** Aurora Kinases are a family of serine/threonine kinases (Aurora Kinases (Aurora A, B, and C) critical for mitosis. Elevated AK expression occurs in a high percentage of melanoma, colon, breast, ovarian, gastric, and pancreatic tumors; in a subset of these tumors the AURKA locus (20q13) is amplified. SNS-314 is a selective pan-AK inhibitor with low nanomolar IC50s. **Methods:** Study design is 3+3 phase 1 dose escalation by modified Fibonacci. Patients (pts) with advanced solid tumors received SNS-314 by 3 hour infusion qweek X 3 (28 day cycle). Primary endpoints: safety, tolerability, and DLT assessment. Secondary endpoints: MTD, pharmacokinetics (PK), pharmacodynamics, and antitumor activity. Pharmacodynamic endpoint was inhibition of Histone H3 phosphorylation (pHH3) evaluated by immunohistochemistry of skin punch biopsies taken pre- and 2 hours post-infusion. **Results:** Thirty-two pts (16M/16F; median age = 58.5 years) were enrolled into 8 cohorts: dose range 30-1800 mg/m<sup>2</sup>. Median cycles received = 2. SNS-314 was generally well tolerated with Grade 1-2 toxicities ≥ 15% incidence: nausea (47%), fatigue (38%), vomiting (28%), constipation (25%), diarrhoea (21%), and tachycardia, anaemia, headache and anxiety (16% each). There were no Grade 3+ toxicities ≥ 5% incidence. There was one DLT of Grade 3 neutropenia preventing administration of all 3 doses of SNS-314. Plasma PK were dose proportional for exposure with no accumulation of SNS-314 following weekly administration. Clearance was moderate (5.65 L/hr/m<sup>2</sup>, CV 39.4%); Vss approximated total body water (21.5 L/m<sup>2</sup>, CV 78.1%); terminal half-life was 10.4 hours (CV 66.8%). Six patients had stable disease as their best response. Inhibition of pHH3 by SNS-314 was observed in skin biopsies of patients treated at doses of 240 mg/m<sup>2</sup> and greater. **Conclusions:** SNS-314 is a novel inhibitor of AKs A, B, and C. The compound has been generally well tolerated; MTD was not established. No objective responses were observed. Pharmacodynamic activity was demonstrated by inhibition of pHH3 at doses of 240 mg/m<sup>2</sup> and greater.

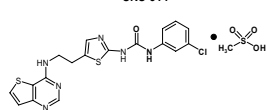
## BACKGROUND



### Aurora A and B Are Required for Successful Mitosis

**Aurora A** controls centrosome maturation and mitotic spindle formation  
**Aurora B** ensures chromosome segregation and alignment as part of the chromosomal passenger protein complex  
**Aurora C** is thought to function similarly to Aurora B

### SNS-314



### SNS-314 In Vitro Profile

- Aurora A IC50 9 nM
- Aurora B IC50 31 nM
- Aurora C IC50 3 nM
- EC50 cell proliferation 1.8-24.4 nM and EC50 induction of polyploidy (>4N DNA) 4.2-93 nM in a diverse panel of human cancer cell lines

## STUDY OBJECTIVES AND TRIAL DESIGN

### Study objectives:

Primary: to determine the safety and tolerability of SNS-314 administered as a 3 hour infusion once a week for 3 consecutive weeks followed by a rest week  
 Secondary: to determine the Maximum Tolerated Dose (MTD), SNS-314 PK, potential pharmacodynamic correlates, and assessment of antitumor activity

### Trial Design:

Phase 1 dose escalation study with standard 3 + 3 design with cohorts of 3-6 patients/cohort. SNS-314 administered as a weekly 3 hour infusion x 3 weeks with one rest week (cycle length of 28 days). Patients received SNS-314 treatment until progression or discontinuation for other protocol defined reasons. Tumor response was evaluated every 2 cycles following Cycle 2. PK were characterized for day 1 and 15 doses. The pharmacodynamic marker of activity, inhibition of phosphohistone H3 (pHH3), was evaluated in skin punch biopsies obtained at baseline and following infusion on day.

### Major Inclusion Criteria:

Written informed consent  
 Age ≥ 18 year  
 Advanced solid tumor for which no satisfactory treatment exists  
 Adequate hematologic, renal, and hepatic parameters

### Major Exclusion Criteria:

Uncontrolled CNS metastases  
 History of arrhythmia or prolonged QTc interval; medications which prolong QT interval  
 Recent myocardial infarction, CVA  
 Allergies to cyclodextrin (Captisol®)

## DEMOGRAPHICS

Age (range)	58.5 (37 – 73)
Sex	50% Male 50% Female
Race	69% Caucasian 16% African-American 9% Asian 6% Native American

## TUMOR TYPES N=32 Patients

Type	N
Non small Cell Lung Cancer	9
Mesothelioma	3
Ductal Carcinoma	2
Sarcoma	3
Ovarian Cancer	2
Pancreas Cancer	4
Endocervical Cancer	1
Poorly Differentiated Cancer	1
Anal Carcinoma	1
Adenocystic Carcinoma	1
Small Cell Lung Cancer	2

## GRADE 1 AND 2 ADVERSE EVENTS (AEs) ≥ 15% (N=24) AND SERIOUS AEs (SAEs) N=3

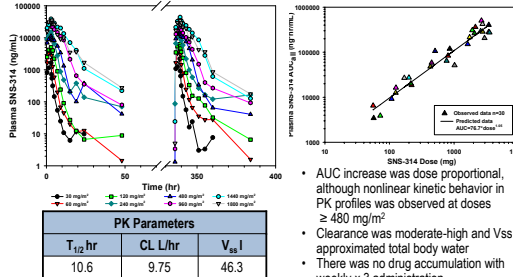
Grade 1 or 2 AE	N(%)	Serious AE (SAE)	N(%)
Nausea	15(47%)	Grade 2 Anemia	1(3%)
Fatigue	12(38%)	Grade 3 Colitis	1(3%)
Vomiting	9(28%)	Grade 3 Cerebrovascular Event	1(3%)
Constipation	8(25%)		
Diarrhea	7(21%)		
Tachycardia	5(16%)		
Anemia	5(16%)		
Headache	5(16%)		
Anxiety	5(16%)		

## SNS-314 EFFECTS ON QTcF WERE NOT CLINICALLY SIGNIFICANT

Dose mg/m <sup>2</sup>	N	Max. QTcF Change From Baseline (msec)			Maximum QTcF Post-Dose (msec)		
		1-29	30-60	> 60	≤ 450	451-480	481-500
30	3	2	1	0	3	0	0
60	3*	0	2	0	3	0	0
120	5*	2	2	0	5	0	0
240	4*	1	2	0	3	1	0
480	4	3	1	0	3	1	0
960	3*	0	1	1	1	2	0
1440	6*	1	4	0	3	2	1
1800	4*	0	2	1	1	3	0

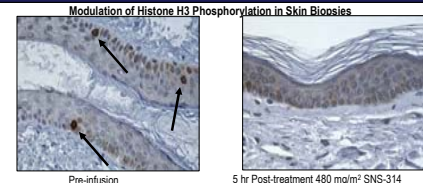
\*Baseline value missing for one patient.  
 Although increases in QTcF were observed, QTcF did not exceed 500 msec for any patient.

## PHARMACOKINETICS



• AUC increase was dose proportional, although nonlinear kinetic behavior in PK profiles was observed at doses ≥ 480 mg/m<sup>2</sup>  
 • Clearance was moderate-high and Vss approximated total body water  
 • There was no drug accumulation with weekly x3 administration

## PHARMACODYNAMICS: SNS-314 DECREASES pHH3 IN PATIENT SKIN BIOPSIES



Dose (mg/m <sup>2</sup> )	Decreased pHH3 After Tx	Pre-dose pHH3 (positive cells/field)	5 hr Post-dose pHH3 (positive cells/field)
240	Y	1.4	0.7
	Y	1	0
	Y	4.7	0.7
	N*	0.6	0.1
480	N*	0.5	0.6
	Y	3.0	0.7
	Y	3.0	0
960	Y	2.9	0.5
	Y	1.7	0.3
1440	Y	3	0.2
	N*	0.2	0
1800*	Y	1.3	0.3
	Y	5	3
	Y	2.25	2

\* Low initial counts precluded detection of significant drop in post-dose signal  
 \* Sample with high background excluded from analysis  
 pHH3 positive cells exhibited intense staining in >50% of nuclear area; positive cells/field indicates number of positively staining cells per high-powered (x100x) field

## EFFICACY PER RECIST (N=28)

Complete/Partial Response	0
Stable Disease	6
Progressive Disease	22

## CONCLUSIONS AND FUTURE DIRECTIONS

- SNS-314 was generally well tolerated in this patient population; MTD was not established
- SNS-314 effects on QTcF were not clinically significant; QTcF did not exceed 500 msec
- Pharmacokinetics were dose proportional for AUC
- Pharmacodynamic modulation of pHH3 in skin biopsies was observed in most patients following treatment with SNS-314 at doses of 240 mg/m<sup>2</sup> or higher
- Further evaluation of SNS-314 at higher doses is warranted based on safety and pharmacodynamic activity but would require further formulation development of the SNS-314 drug product