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Results of Two Phase 1 Dose Escalation Studies of the Oral Heat Shock Protein 90 (Hsp90) Inhibitor SNX-5422

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BACKGROUND

- Heat shock protein 90 (Hsp90) is a molecular chaperone that is exploited by cancer cells for at least two purposes:
  - To activate and stabilize labile forms of oncoproteins, including many kinases and transcription factors, that have undergone biochemical transformations (mutation, translocation, amplification, overexpression); and
  - To act as a buffer against the cellular stresses essential for cancer cell survival.[1]
- Hsp90 inhibition has shown clinical activity in cancers addicted to particular driver oncogenes, such as HER2, EML4-ALK, and mutated EGFR.[1]
- SNX-5422 is an orally bioavailable prodrug of SNX-2112, which is a highly potent, non-geldanamycin analog Hsp90 inhibitor.[2]
- SNX-5422 has extended tumor residence time and has demonstrated significant antitumor activity in multiple mouse xenograft models of human tumors, including lung, breast, and multiple myeloma.[3-5]
- Two Phase 1 studies have been conducted in patients with refractory solid tumor malignancies or non-Hodgkin's lymphoma (reported here).

OBJECTIVES

Primary

- To evaluate safety of SNX-5422, including determination of dose limiting toxicities (DLTs) and maximum tolerated doses (MTDs).

Secondary

- To characterize the pharmacokinetics (PK) of SNX-5422 and its active metabolite, SNX-2112.
- To investigate the tumor response to SNX-5422.

METHODS

Study Design

- Two Phase 1, multicenter, open-label, 3+3 dose-escalation studies.
- *SNX-5422-CLN1-001:* SNX-5422 administered (a) once daily every day (QD) for 28 out of 28 days, or (b) QD for 21 out of 28 days, followed by 7-day period without study drug, or (c) once daily every other day (QOD) for 21 out of a 28-day cycle, followed by 7-day period without study drug.
  Dosing schedule:
  - 50 mg/m^2 QD x 28 days
  - 50 to 89 mg/m^2 QD x 3 weeks on/1 week off
  - 4 to 100 mg/m^2 QOD x 3 weeks on/1 week off
- *SNX-5422-CLN1-004:* SNX-5422 administered QOD for 21 days out of a 28-day cycle.
  Dosing schedule:
  - 100 to 133 mg/m^2 QOD x 3 weeks on/1 week off
- Actual dose administered was based on body surface area, calculated via actual body weight at start of each cycle; calculated dose then rounded to nearest mg on dosing chart.
- Concomitant medications were to be taken ≥1 hour before or 2 hours after SNX-5422, except agents with clinically-relevant cytochrome P450 (CYP) 3A4 metabolism that were to be taken at least 3 hours before or 3 hours after SNX-5422.

Key Eligibility Criteria

- Males or non-pregnant, non-breastfeeding females ≥18 years-of-age with histologically confirmed, non-CNS, solid tumor malignancy or Non-Hodgkin's lymphoma refractory to available therapy or for which there was no available therapy.
- Karnofsky performance score ≥60, life expectancy ≥3 months, and adequate baseline laboratory values.
- No uncontrolled known brain metastases, spinal cord compression, carcinomatous meningitis, or leptomeningeal disease.
- No anticancer therapy currently or within the 28 days or 5 half-lives (whichever was shorter) before study entry, and all adverse events (AEs) recovered to at least ≤ Grade 1 toxicity level.
- No gastrointestinal (GI) diseases or conditions (including chronic diarrhea) affecting drug absorption (including gastric bypass) or safety assessments (e.g., Crohn's disease, irritable bowel syndrome).
- No glaucoma, retinitis pigmentosa, macular degeneration, or any retinal changes detected by ophthalmological examination.

Safety and Efficacy Analysis

- Adverse event data for the 2 studies were combined.
- Efficacy data from the QOD (3 weeks on/1 week off) population in Study SNX-5422-CLN1-001 was combined with data from Study SNX-5422-CLN1-004; other dosing groups from SNX-5422-CLN1-001 were analyzed separately.
- Tumor response was assessed every 8 weeks using RECIST 1.1 criteria for solid tumors or the Lymphoma Response Criteria for lymphomas (version 1.0). Only patients with post-baseline disease assessment data are included in the tabulation of best response to treatment.

Pharmacokinetic Analysis

- Serial blood samples for the main PK analyses of SNX-5422 and SNX-2112 were collected within 4 hours pre-dose and up to 24-48 hours post-dose on Day 1 and Day 21 of Cycle 1.
- PK parameters calculated using non-compartmental methods; data then summarized.

RESULTS

Table 1. Baseline Characteristics

Parameter	N=56
Age, median (range), years	61 (37-80)
Age >65 years, n (%)	23 (41%)
Males, n (%)	34 (61%)
Race, n (%)	
White	51 (91.1%)
Hispanic or Latino	3 (5.3%)
Black or African-American	2 (3.6%)
Primary Tumor, n (%)	
Prostate	11 (19.6%)
Breast	6 (10.7%)
Colon	6 (10.7%)
Rectal	4 (7.1%)
Lung (NSCLC)	4 (7.1%)
Other*	25 (44.6%)
Prior treatments, n (%)	
Prior systemic therapy (no. regimens)	
0	2 (3.6%)
1-3	17 (30.4%)
>3	37 (66.1%)
Radiotherapy/radiosurgery	20 (35.7%)

* Adrenal gland, anal, bladder, choroidal melanoma, colorectal, endometrial, esophageal, gastrointestinal, GIST, hepatocellular, melanoma, neuroendocrine, pancreas, salivary gland, testicular, thyroid, unknown

Table 2. Dosing Cohorts

Cohort/ Dosing Schedule	Dose (mg/m^2)	Number of Patients Assigned to Cohort	DLT (Cycle 1)
SNX-5422-CLN1-001		N=47	
QOD (21/28 days)			
1	4	3	
2	5.32	3	
3	10.64	4	
4	21.28	4	
5	42	4	
6	56	4	
7	100	5	
QD (21/28 days)			
8	50	6	n=1 (diarrhea Grade 3)
9	67	7	n=1 (diarrhea Grade 3)
10	89	3	n=2 (diarrhea Grade 3)
11*	67	1	
QD (28/28 days)			
12	50	3	n=1 (GI hemorrhage Grade 3)
SNX-5422-CLN1-004		N=9	
QOD (21/28 days)			
1	133	3	n=2 (diarrhea Grade 3)
2	100	6	

QOD=every other day; QD=once daily.
*Patient received 7 doses QD, then switched to QOD schedule during Cycle 1.

Maximum Tolerated Doses

- With the QD dosing regimen, 2 patients on 89 mg/m^2 experienced DLTs; therefore, the MTD was determined to be 67 mg/m^2 QD (study SNX-5422-CLN1-001).
- At 133 mg/m^2 QOD, 2 patients experienced DLTs; therefore, 100 mg/m^2 QOD was defined as the MTD and that cohort was expanded (study SNX-5422-CLN1-004).

SAFETY

Exposure

SNX-5422-CLN1-001

Exposure was ≤ 20 to 59 days for most (64%) patients; mean exposure = 80.4 days (range: 1-598 days).

Last treatment cycle for most (72%) patients was Cycle 1, 2, or 3; mean = 3.4 cycles (range: 1-22 cycles).

SNX-5422-CLN1-004

Exposure was 40 to 59 days for most (67%) patients; median = 21 days (range: 3-23 days).

Last treatment cycle for most (67%) patients was Cycle 2.

Table 3. Summary of Adverse Events

Adverse Event (AE)	Number of Patients (%) N=56
At least one treatment-emergent AE	56 (100%)
Treatment-related AE	53 (95%)
Grade 3 or 4 treatment-emergent AE	25 (45%)
Grade 5 AE (death)*	4 (7%)
Serious AE (SAE)	17 (30%)
Treatment-related SAE	3 (5%)
AEs leading to study discontinuation	13 (23%)
AEs leading to dose interruption	16 (29%)
Dose limiting toxicity	7 (13%)

* These included septic shock, cardio respiratory arrest, multi organ failure (none related), and treatment-related intestinal perforation.

Table 4. Most Frequent Treatment-Related Adverse Events* by Dose Schedule and Grade

Adverse Event	QOD schedule (n=36; 4-133 mg/m^2)		QD schedule (n=17; 50-89 mg/m^2)		Total (N=56†)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
	Number of Patients		Number of Patients		Number of Patients	
Diarrhea	17	2	11	4	30	6
Nausea	15	0	5	0	22	0
Fatigue	9	0	7	0	16	0
Vomiting	9	0	5	0	16	0
Abdominal pain	4	0	4	0	8	0
Anorexia	5	0	3	0	8	0
Dry mouth	2	0	3	0	5	0
Anemia	2	1	0	1	3	2

QOD=every other day; QD=once daily.
* Reported by ≥10% of patients overall.
†Includes 3 patients from the 50 mg/m^2 QD continuous dosing cohort.

- QD dosing regimen was associated with higher incidences of treatment-related AEs, with 20 patients experiencing 168 AEs vs. 36 patients experiencing 141 AEs on the QOD schedule.

Dose Limiting Toxicities (DLTs)

- 7 patients had DLTs, all Grade 3; most common DLT was diarrhea, with 6 incidences; there was 1 Grade 3 nictalopia (visual darkening). DLTs in 2 patients were SAEs (1 diarrhea and 1 GI hemorrhage).
- Events resolved in all patients, except 1 patient with Grade 2 dehydration.

Visual Adverse Events

- 4 patients had treatment-related nictalopia (visual darkening) and 1 had treatment-related blurry vision; all events were reversible, with complete recovery within a few days to a week following treatment discontinuation.
  - Nictalopia (visual darkening): 4 patients, Grade 1 to 3, with QD doses of 50 to 89 mg/m^2; led to treatment discontinuation in 2 patients (1 on 89 mg/m^2 QD and 1 on 50 mg/m^2 QD continuous, who also had photophobia).
  - Blurry vision (Grade 1): 1 patient on 100 mg/m^2 QOD, retrospectively reported after dark adaptometry, showed an elevated threshold from Screening.

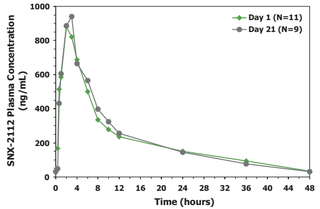
PHARMACOKINETICS

Table 5. Mean (±SD) SNX-2112 Pharmacokinetic Parameters for Day 21 (SNX-5422-CLN1-001 & 004)

Evaluable for PK	Dose (mg/m^2)	T_{max} (hr)*	C_{max} (ng/mL)	$T_{1/2}$ (hr)	$AUC_{0\text{-}last}$ (hr•ng/mL)
QOD Cohorts					
N=2	4	0.9 (0.7-1.0)	31 ± 15	9.9 ± 0. 7	193 ± 40
N=3	5.32	2.0 (2.0-3.0)	42 ± 18	9.2 ± 0.8	451 ± 224
N=3	10.64	1.0 (0.7-1.0)	219 ± 219	12.4 ± 6.1	2410 ± 2770
N=3	21.28	3.0 (0.7-6.0)	460 ± 143	16.8 ± 3.6	6610 ± 4000
N=3	42	3.1 (1.0-6.0)	464 ± 272	15.1 ± 7.8	5340 ± 3550
N=3	56	2.0 (1.6-3.0)	770 ± 333	10.9 ± 1.3	6010 ± 3740
N=11	100	2.0 (0.8-4.0)	1220 ± 707	10.2 ± 2.1	10500 ± 8410
N=0	133	NR	NR	NR	NR
QD Cohorts					
N=6	50	1.6 (1.0-3.0)	579 ± 259	11.1 ± 1.6	3950 ± 1960
N=4	67	2.6 (1.0-4.0)	723 ± 233	9.8 ± 1.7	5770 ± 2120
N=1	89	NR	NR	NR	NR

T_{max}=time to maximum plasma concentration; C_{max}=maximum plasma concentration; AUC=area under the plasma concentration-time curve; QD=once daily; QOD=once every other day; SD=standard deviation; NR=not reported. Median and (range) reported for T_{max}.

Figure 1. Mean SNX-2112 Plasma Concentration-time Profiles on Day 1 and Day 21 of Treatment Cycle 1 for 100 mg/m^2 QOD



Pharmacokinetic Conclusions

- SNX-5422 (prodrug) rapidly converted to its active metabolite, SNX-2112. As expected, most samples collected post-dose showed no measurable concentrations of SNX-5422. Concentrations of SNX-2112 were detected as early as 0.33 hours after dosing.
- Peak concentrations of SNX-2112 following QOD and QD dosing were generally observed between 0.7 and 3.0 hours after dosing for both Day 1 and Day 21.
- SNX-2112 exhibited a relatively short terminal half-life ($T_{1/2}$) in plasma. $T_{1/2}$ was similar across all cohorts in both studies, indicating that $T_{1/2}$ appears independent of dose and dosing regimen. Overall, mean $T_{1/2}$ in both studies ranged from 8.5 to 15.6 hours on Day 1 and from 9.2 to 16.8 hours on Day 21.
- SNX-5422 at QOD doses ranging from 4 to 100 mg/m^2 and QD doses ranging from 50 to 89 mg/m^2 produced dose-related increases in SNX-2112 exposures. C_{max} and AUC_{last} generally increased in a linear manner with increasing dose; however, increases were greater than dose proportional.
- Comparison of SNX-2112 exposures on Day 1 and Day 21 showed minimal to no accumulation of SNX-2112 in plasma following either QOD or QD dosing for 21 days. There was no evidence of accumulation of SNX-2112 at the MTD of 100 mg/m^2 QOD.

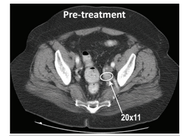
EFFICACY

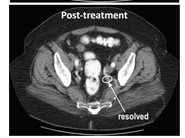
Antitumor Activity

- Antitumor activity was assessed in 43 patients (as 13 patients had no post-baseline tumor assessment data).
- Objective responses were observed (all on a QOD schedule) in:
  - 1 patient with prostate cancer (durable, complete response on 56 mg/m^2 QOD - see Case History).
  - 1 patient with adrenal cancer (unconfirmed partial response for 2 cycles on 5.32 mg/m^2 QOD).
  - 1 subject with breast cancer (partial response for 8 cycles on 56 mg/m^2 QOD).
- Stable disease was observed in 12 of 32 patients (38%) on a QOD schedule and in 7 of 11 patients (64%) on a QD schedule.
- Noteworthy stable disease was observed in:
  - 2 patients with neuroendocrine cancer (1 with liver/lung lesions on 100 mg/m^2 QOD and 1 with pancreatic lesions on 42 mg/m^2 QOD); both received 8 cycles before withdrawing from the study with stable disease.
  - 1 patient with hepatocellular cancer (on 42 mg/m^2 QOD) who received 6 cycles before withdrawing from the study.
  - 4 patients with stable disease for more than 4 cycles: 2 with prostate cancer (on 42 mg/m^2 QOD, and on 67 mg/m^2 QD), 1 with GIST (on 56 mg/m^2 QOD), and 1 with carcinoid of the small bowel (on 50 mg/m^2 QD).

Case History

- 69-year old Caucasian male, diagnosed with prostate cancer in June 1998.
- Progressive disease after 4 regimens of systemic anticancer therapy, ending June 2008.
- Started SNX-5422 56 mg/m^2 QOD in July 2008.
- 100% reduction of all target lesions (lymph nodes) reached in Cycle 8; prostate-specific antigen level = 0 ng/mL.
- Subject withdrew in Cycle 22 with complete response (100% reduction) in March 2010.
- Treatment was well-tolerated, with manageable diarrhea throughout treatment, and gastroesophageal reflux disease and duodenitis beginning at 1 year of treatment; all events were Grade 1.





CONCLUSIONS

- The MTDs were established at 67 mg/m^2 for QD, and 100 mg/m^2 for QOD.
- SNX-5422 monotherapy was generally well-tolerated at doses up to 67 mg/m^2 QD and 100 mg/m^2 QOD.
- Diarrhea was the most common AE and most common DLT event, but caused study discontinuation in only 2 patients (1 on 89 mg/m^2 QD and 1 on 133 mg/m^2 QOD). There were 8 incidences of dose interruption in 6 patients due to diarrhea.
- Treatment-related ocular toxicity appears to be schedule dependent and reversible, and was primarily observed with QD dosing [4 cases of nictalopia (visual darkening) at 50–89 mg/m^2 QD]. Nictalopia was not seen with QOD dosing. There was 1 case of blurry vision (Grade 1) that was retrospectively reported after dark adaptometry examination in a patient on QOD dosing.
- SNX-5422 monotherapy showed promising signs of clinical activity in patients with refractory solid tumors.
- Based on the superior benefit-risk profile of QOD dosing over QD dosing as observed in present preliminary clinical findings, 100 mg/m^2 QOD has been selected for further clinical testing.

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