A phase I dose escalation study of oral SB939 when administered thrice weekly (every other day) for 3 weeks in a 4-week cycle in patients with advanced solid malignancies

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Background:

- Aberrant histone acetylation may lead to transcriptional dysregulation of genes involved in the control of cell cycle progression, differentiation and apoptosis, and is implicated in the development of cancer.
- SB939 is a potent competitive inhibitor of Class 1 and 2 histone deacetylase (HDAC).
- The antitumor activity has been demonstrated in several xenograft mouse models of solid and hematological malignancies including colorectal cancer, ovarian cancer, prostate cancer, AML and B cell lymphoma.

Objectives:

Primary

- To assess the safety and tolerability of SB939, administered orally once daily every other day 3 times a week for 3 consecutive weeks, repeated every 4 weeks, in patients with advanced solid tumours.

Secondary

- To Establish the maximum tolerated dose (MTD) and recommended Phase II dose (RD).
- To determine the pharmacokinetic profile of SB939.
- To document preliminary efficacy of SB939 in patients with advanced solid malignancies.

Methods:

Study design

- A phase I, first-in-man, multicenter, open-label, dose-escalation study of SB939 in 2 stages.
  - Stage 1 – assess escalating doses of cohorts.
  - Stage 2 – 6 to 10 additional patients at recommended Phase II dose.
- Patients remained in the study until disease progression (RECIST), unacceptable toxicities occurred or patient withdraw consent.
- The starting dose of 10 mg was derived from 1/10th the NOAEL in dog.
- First cycle DLT were used in dose escalation decisions.

Patient selection

- Patients with histologically proven solid tumour refractory to standard therapy or for which no standard therapy exist. Adequate performance status, life expectancy and organ function.
- Exclusion criteria include significant cardiac event within 1 year, prolonged QTc interval, brain metastasis, malabsorption, concomitant valproic acid or other HDAC inhibitor.

MTD and RD definition

- The Maximum Tolerated Dose (MTD) is defined as the lowest dose level at which 2 or more patients out of 6 patients, who have completed at least one cycle of treatment, experience unacceptable (DLT) toxicity.
- The recommended dose for Phase II studies (RD) is defined as the next dose level below the MTD.

Pharmacokinetic assessment

- Samples for pharmacokinetic profile drawn prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24±2 and 30 ±2 hours after dosing on Day 1 (dose 1) and 15 (dose 7)
- SB939 concentrations in plasma were determined using a validated LC-MS/MS method.
- Non-Compartmental Analysis using WinNonLin, Version 5.1 (Pharsight) method for pharmacokinetic analysis.

Biomarker assessment

- Levels of AcH3 in PBMCs from peripheral blood cells were determined using a validated western blot.

Efficacy

- Tumour assessments were performed at baseline and after every 2 cycles of treatment using RECIST criteria.
- In patients discontinuing without disease progression, tumor assessments were undertaken every 3 months until disease progression occurs or post-study anti-cancer treatment is initiated.

Table 1: *Patient characteristics*

	Number of patients
Total enrolled	28
Gender (%)	
Male	13 (46)
Female	15 (54)
Age (years)	
Median	57
Range	41-73
ECOG performance status (%)	
0	12 (42.9)
1	13 (46.4)
2	3 (10.7)
Disease	
Colorectal	10
Breast	4
Hepatocellular carcinoma	4
Sarcoma	3
Endometrial	2
Gastric	1
Others	4
Prior systemic treatment regimens	
≤1	11
2	9
3	2
≥4	6

Results:

- As of 15 Aug 2008, twenty eight patients (13 males, 15 females) were recruited. The characteristics of the patient population are presented in Table 1.
- Median number of cycles treated was 3.6 cycles.
- Six patients are still on active treatment.
- Reasons for study discontinuation include: disease progression (n=18), withdrawal of consent (n=3), and adverse events (n=1). Treatment related adverse event (QTc prolongation) accounted for study discontinuation in 1 patient.

Table 2: *Dose levels studied and corresponding DLT*

Dose level cohort (mg)	Patients enrolled	Treatment ongoing	Dose limiting toxicities
10	3	0	-
20	4	0	-
40	8	0	Fatigue G3 (n=1)
60	7	5	Hypokalaemia G3 (n=1)
80	6	1	Troponin T increased G3 (n=1), fatigue G3 (n=1), QTc prolongation G3 (n=1)

- DLTs were observed in 1 out of 8 patients at 40 mg, 1 out of 7 patients at 60 mg and 3 out of 6 patients at 80 mg. Dose levels and corresponding DLTs are shown in Table 2.
- Toxicities were manageable with fatigue, anorexia, nausea and vomiting most frequently observed (Table 3).

Fig 1: *Oral concentration-time profiles of SB939 on Day 1 and 15. Error bars are ± SEM*

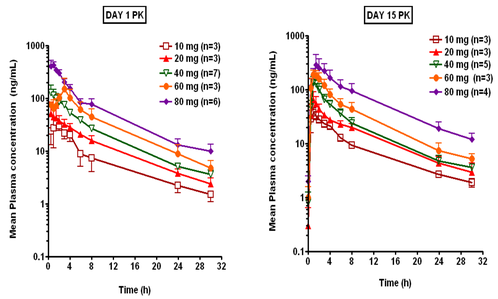
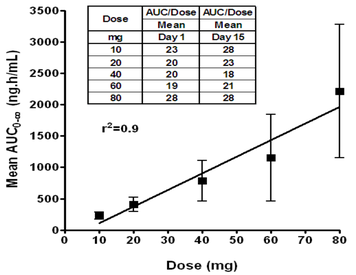


Table 3: *Most common treatment related toxicities (highest grade per event per patient, n=27)*

Adverse events	Grade 1/2		Grade 3/4	
	No. of patients	(%)	No. of patients	(%)
Haematologic				
Thrombocytopenia	2	(7)	2	(7)
Anaemia	0	(0)	1	(4)
Non-haematologic				
Fatigue	15	(56)	2	(7)
Anorexia	10	(37)	0	(0)
Vomiting	9	(33)	0	(0)
Nausea	8	(30)	0	(0)
Diarrhoea	4	(15)	0	(0)
Hypokalaemia	3	(11)	1	(4)
ECG	1	(4)	1	(4)
Troponin T	1	(4)	1	(4)

Fig 2: *Relationship of mean $AUC_{0-\infty}$ with dose. Error bars are ± SD. Table in inset shows the relationship of AUC/Dose with Dose*



- SB939 is rapidly absorbed and followed bi-exponential disposition (Fig 1).
- C_{max} and AUC $_{(0-\infty)}$ were dose-proportionally increased over the range studied (Fig 2).
- There was no accumulation of SB939 following repeated dosing.
- The mean plasma concentrations of SB939 were above its HDAC enzyme IC_{50} ($T>IC_{50}$) for 12 and 24h in 40 and 80 mg cohorts, respectively.

Fig. 3: *Western blots from 60 mg cohort*

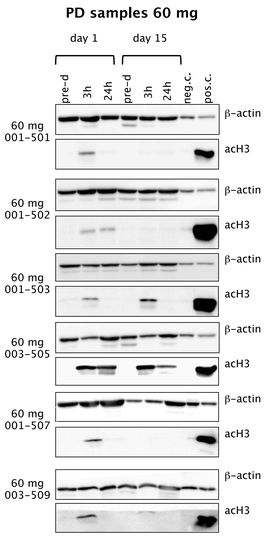
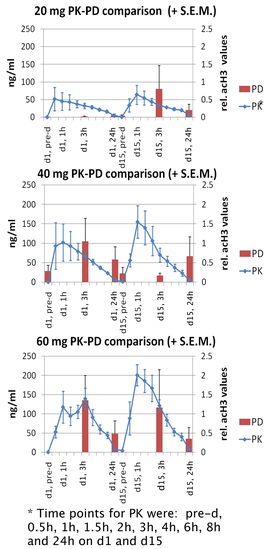


Fig. 4: *PK-PD comparison for 20 mg, 40 mg and 60 mg*



* Time points for PK were: pre-d, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h and 24h on d1 and d15

Table 4: *Pharmacokinetic parameters of SB939 on day 1 and 15*

PK Parameters	10 mg		20 mg		40 mg		60 mg		80 mg	
Dose	Day-1	Day-15	Day-1	Day-15	Day-1	Day-15	Day-1	Day-15	Day-1	Day-15
C_{max} (ng/ml)	39 ± 16	40 ± 13	61 ± 46	70 ± 36	158 ± 101	150 ± 82	172 ± 128	209 ± 57	472 ± 230	361 ± 230
T_{max} (h)	1.8 ± 1.9	1.0 ± 0.5	2 ± 2	2 ± 1	1.1 ± 1.3	1.3 ± 0.3	1.8 ± 1	1.0 ± 0.5	0.9 ± 0.4	1.6 ± 1.0
$T_{1/2}$ (h)	6.8 ± 0.2	9.4 ± 1.4	8.2 ± 0.5	7.6 ± 1.9	7.0 ± 0.9	7.1 ± 1.3	6.9 ± 0.3	6.9 ± 0.8	7.3 ± 1.3	8.1 ± 2.1
V_d/F (L)	442 ± 102	481 ± 20	616 ± 191	471 ± 51	587 ± 218	634 ± 200	641 ±300	536 ±220	490 ± 318	564 ± 385
CL/F (L/h)	45 ± 11	36 ± 7	52 ± 15	45 ± 13	59 ± 23	63 ± 22	64 ± 29	54 ±19	45 ±24	45 ± 23
$AUC_{0-\infty}$ (ng.h/ml)	229 ± 53	283 ± 50	408 ± 113	468 ± 125	785 ± 327	722 ± 321	1151 ± 690	1244± 535	2215 ± 1062	2244 ± 1281

- Acetylated Histone 3 level in PBMC corresponds to systemic exposure of SB939 (Fig 4)
- Of the 18 patients evaluable for response, stable diseases were seen in 4 patients (breast, colorectal, follicular thyroid and hepatocellular carcinoma). The duration of response ranged from 55 to 220 days.

CONCLUSION:

- SB939 has a manageable toxicity and favourable pharmacokinetic profile.
- The 80 mg dose was the highest dose tested in this study and was not tolerated by 3 out 6 patients.
- 60 mg is the recommended dose for Phase II studies in patients with solid tumour.
- A total of 10 patients were planned for this cohort.