Phase 1 Study of the Oral Deacetylase Inhibitor, SB939, in Patients with Advanced Hematologic Malignancies

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2010 ASH Annual Meeting
Abstract # 3292

BACKGROUND

- SB939 is a novel orally bioavailable inhibitor of class 1, 2, and 4 histone deacetylases (HDACs)
- SB939 has demonstrated antitumor activity in xenograft models of AML (MV4-11) and B-cell lymphoma (Ramos) as well as in models of solid tumors
- In all tested *in vivo* models, SB939 showed dose-dependent antitumor effects and was well tolerated at doses up to 100 mg/kg
- In human tumor cell lines, SB939 inhibits proliferation and promotes apoptosis at an IC_{50} of 0.1 – 1.3 μM
- Lymphomas and tumors of hematological origin show the highest sensitivity to SB939

STUDY OBJECTIVES

Primary

- Assess the safety and tolerability of SB939, administered orally once every other day 3 times a week for 3 weeks, repeated every 4 weeks, in subjects with advanced hematologic malignancies

Secondary

- Establish the MTD and recommended Phase 2 dose of SB939 when administered as a single agent according to the study regimen
- Determine the dose-limiting toxicities (DLTs) of SB939
- Determine the pharmacokinetic (PK) profile of SB939
- Assess histone acetylation in PBMCs as well as other biomarkers
- Document anti-tumor activity

STUDY DESIGN

- Phase 1, multi-center, open-label, escalating dose cohort study
- Subjects were treated at one dose level for a minimum of 2 months (2 cycles) and a maximum of 1 year
- Dose cohorts began at the 10 mg level
- Response assessments were performed as clinically indicated using bone marrow biopsy and/or aspirate
- Identification of the MTD was based on safety data from evaluable subjects in Cycle 1

PATIENT SELECTION

Key eligibility criteria:

- Hematologic malignancy (refractory or relapsing leukemia, high-risk myelodysplastic syndrome [MDS], multiple myeloma [MM], myelofibrosis [MF], non-Hodgkin's lymphoma [NHL], or Hodgkin's disease)
  - Must have failed, relapsed, or been ineligible for standard effective therapy or peripheral blood stem cell transplantation;
- Age ≥ 18 years
- ECOG performance status 0, 1, 2
- Life expectancy ≥ 3 months
- Adequate hepatic, renal, and cardiac function
- No clinically significant co-morbidities
- Corrected QT interval (QTc) ≤ 450 ms (men) or ≤ 470 ms (women)

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Parameter	(N = 44)
Median age, years (range)	70 (37-84)
Male/Female	25/19
Acute myelogenous leukemia Myelodysplastic syndrome (IPSS Intermediate 1) Myelodysplastic syndrome (IPSS Intermediate 2) Myelodysplastic syndrome (IPSS High) Follicular lymphoma Mantle cell lymphoma Non-Hodgkin's lymphoma Primary myelofibrosis Myelomonocytic leukemia	25 8 3 3 1 1 1 1 1
ECOG performance status	0 = 30% 1 = 59% 2 = 11%
No. of prior systemic therapy regimens, median (range)	2 (0-9)
Received transplant	7 (16%)

PATIENT DISPOSITION (as of November 2010)

	N
Enrolled	44
Evaluable for safety (received at least one dose)	44
Evaluable for response	30
Median time on study drug, days (range)	48 (3-327)
Patients on study drug ≥ 3 months	11
Discontinued treatment prior to 1 year ▪ Disease progression ▪ Adverse event ▪ Investigator/patient preference ▪ No response ▪ Death	41 21 6 5 5 4

TREATMENT-RELATED ADVERSE EVENTS WITH A TOTAL INCIDENCE ≥ 10%

Adverse Event	Grade 1/2	Grade 3/4	All Grades
Fatigue	17 (38%)	5 (11%)	22 (50%)
Nausea	15 (34%)	0	15 (34%)
Anorexia	9 (20%)	1 (2%)	10 (23%)
Diarrhea	6 (14%)	1 (2%)	7 (16%)
Thrombocytopenia	1 (2%)	6 (13%)	7 (16%)
Vomiting	6 (14%)	0	6 (14%)

TREATMENT-RELATED SERIOUS ADVERSE EVENTS

Dose Level	Subject	Disease	Serious Adverse Event	Severity Grade	Relationship to Study Drug
40 mg	005-1302	AML	Prolonged QTc	3	Probable
60 mg	002-1401	AML	Neutropenic sepsis	4	Possible
			Hypotension	4	Possible
			Respiratory failure, type 1	4	Possible
			Pneumonia	5	Possible
80 mg	004-1502	AML	Fatigue (2 episodes)	3, 3	Possible
100 mg	004-1608	MDS Int-1	Prolonged QTc	3	Possible
	004-1619	MDS Int-1	Acute gastroenteritis	3	Possible
	004-1620	AML	Fatigue	3	Probable
	004-1623	AML	Fatigue	3	Possible
	005-1624	AML	Leg pain	4	Possible
120 mg	002-1701	AML	Neutropenic sepsis	3	Possible
	002-1706	AML	GI hemorrhage (2 episodes)	2, 3	Possible
			Abdominal pain	1	Possible
			Upper bleeding, GIT (2 episodes)	3, 3	Possible
			Pneumonia	3	Possible

DOSE-LIMITING TOXICITIES

DLT criteria (must have occurred during Cycle 1):

- Treatment-related non-hematologic toxicity Grade 3/4 (excluding Grade 3 nausea/vomiting with suboptimal anti-emetic therapy) *[except in subjects with malignant lymphoma]*
- Neutropenia Grade 4 lasting ≥ 7 d or neutropenia Grade 3/4 with fever and/or infection
- Thrombocytopenia Grade 4 (or Grade 3 with bleeding)
- Dose delay > 2 wk or ≥ 4 missed doses because of a treatment-related AE or lab abnormality

Dose Level	No. of DLTs/ Total No. Subjects	DLT
10 mg	0/1	
20 mg	0/1	
40 mg	1/6	Prolonged QTc
60 mg	0/3	
80 mg	0/3	
100 mg	1/6	Prolonged QTc
120 mg	1/6	Neutropenic sepsis

- The MTD as defined was not reached.
- 120 mg declared as the MTD because of dose reductions needed after multiple cycles of treatment.
- 100 mg determined to be the recommended dose for Phase 2.

SAFETY SUMMARY

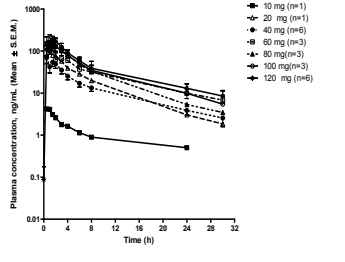
- SB939 was generally well tolerated
- The most common treatment-related toxicities were fatigue (50%), nausea/vomiting (48%), anorexia (23%), diarrhea (16%), and thrombocytopenia (16%)
- The most common treatment-related Grade 3/4 toxicities were thrombocytopenia (13%) and fatigue (11%)
- Dose-limiting toxicities consisted of asymptomatic QTc prolongation (2 subjects), a possible class effect of HDAC inhibitors, and neutropenic sepsis
- The MTD as defined was not reached.
- 100 mg was determined to be the recommended dose for Phase 2

RESPONSE SUMMARY

Response Category	No. of Subjects	Disease	Comment
CR	2	AML	80 mg; duration, 362+ d
		AML	120 mg; duration, 206+ d
PR	0		
SD	12	MDS Int-1 (n=5)	Duration, 35+ to 184+ d
		AML (n=4)	Duration, 56+ to 354+ d
		MDS High	Duration, 72+ d
		1° myelofib. (n=1)	Duration, 141+ d
		Myelom. leuk. (n=1)	Duration, 28+ d
PD	16		

PHARMACOKINETIC ANALYSIS

- SB939 showed rapid absorption and biexponential disposition



PHARMACOKINETIC ANALYSIS (Cont.)

Parameter	10 mg (n=1)		20 mg (n=1)		40 mg (n=6)		60 mg (n=3)	
	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15
T_{max} (h)	0.5	0.5	0.5	1.0	1.1 ± 1	1.3 ± 0.7	1.0 ± 1.0	0.8 ± 0.3
C_{max} (ng/ml)	4.2	7.7	149	110	84 ± 34	64 ± 19	133 ± 117	118 ± 135
AUC $_{0-\infty}$ (ng·h/ml)	38	128	632	562	437 ± 194	478 ±190	955 ± 1145	765 ± 748
$t_{½}$ (h)	16.5	14.4	5.9	7.6	9.5 ± 3.5	10.6 ± 2.4	12.4 ± 2.7	11.6 ± 3.6

Parameter	80 mg (n=3)		100 mg (n=3)		120 mg (n=6)	
	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15*
T_{max} (h)	1.3 ± 0.8	1.2 ± 0.3	1.0 ± 0.3	1.0 ± 1.0	1.2 ± 0.4	1.0
C_{max} (ng/ml)	189 ± 182	164 ± 122	187 ± 99	314 ± 143	202 ± 83	96
$AUC_{0-\infty}$ (ng·h/ml)	1049 ± 805	984 ± 454	1168 ± 348	1960 ± 636	1373 ± 641	762
$t_{½}$ (h)	6.9 ± 1.1	9.1 ± 4.3	8.0 ± 1.0	13.7± 6.0	10.3 ± 3.0	14

Note: Results are expressed as mean ± SD
*** n=2**

- T_{max} ranged between 0.5 and 1.3 hours
- Terminal half-life ranged between 6 and 17 hours
- No accumulation observed on Day 15 compared with Day 1
- Mean AUC and C_{max} showed a dose proportional increase between 40 and 120 mg
- Concentrations above the IC_{50} of SB939 for HDAC 1, 2, and 3 were reached at all dose levels

SUMMARY AND CONCLUSIONS

- SB939 demonstrated excellent pharmacokinetic properties and target inhibition and was generally very well tolerated
- Toxicities were generally mild to moderate in severity and easily managed compared with those associated with other HDAC inhibitors
- The MTD as defined for this regimen of SB939 in subjects with hematologic malignancies was not reached, and 100 mg was determined to be the recommended dose; these findings indicate a favorable therapeutic index
- Response data, particularly in higher-risk MDS and AML, encourage further exploration of the therapeutic benefit of SB939 treatment in combination with other anti-cancer therapies

CONFLICT OF INTEREST STATEMENT

H. J. Zhu and K. Ethirajulu are employees of S*BIO Pte Ltd.

All other authors declare no conflict of interest.