Phase I and pharmacodynamic study of an orally administered novel inhibitor of histone deacetylases, SB939, in patients with refractory solid malignancies

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Background: The objective of this study was to assess the safety, maximum tolerated dose (MTD), pharmacokinetics, pharmacodynamics, and preliminary efficacy of SB939, a novel histone deacetylase (HDAC) inhibitor, in patients with advanced solid malignancies.

Patients and methods: Dose-escalating cohorts of three to six patients received SB939 orally thrice weekly for 3 weeks in a 4-week cycle. Acetylated histone H3 (acH3) was measured in peripheral blood mononuclear cells (PBMCs).

Results: Thirty patients treated at one of five doses (10–80 mg/day) received 79 cycles of SB939 (range, 1–12 cycles). Dose-limiting toxic effects were fatigue, hypokalemia, troponin T elevation, and QTc prolongation. Peak plasma concentration (C_{max}) and area under the concentration–time curve extrapolated to infinity increased dose proportionally. The MTD of SB939 was 80 mg/day. The mean elimination half-life and oral clearance of SB939 were 7.2 ± 0.6 h and 53.0 ± 8.5 l/h, respectively, with no substantial accumulation on day 15. An increase in acH3 was observed at hour 3 and correlated with dose and C_{max}. Stable disease was seen in several tumor types treated at ≥40 mg. HDAC inhibition was consistently observed at 60 mg, the recommended dose.

Conclusions: SB939 can be safely administered at the recommended dose and reaches plasma levels that strongly inhibit HDAC in PBMCs. These data support further efficacy studies of SB939.

Key words: histone deacetylase, pharmacodynamics, pharmacokinetics

introduction

Mammalian histone deacetylases (HDACs) catalyze the removal of acetyl groups from lysine residues and thus regulate the acetylation of histone and nonhistone proteins [1, 2]. HDAC inhibitors, a class of drugs with anticancer properties, cause acetylation of cellular histones and nonhistone proteins. Acetylation of histones modulates gene transcription through relaxation of the chromatin structure and increases the accessibility of transcription factors to target genes [3].

In cancer cells, aberrant epigenetic suppression of gene expression may provide cells with a growth advantage through genes involved in cell cycle regulation, DNA repair, cell signaling, apoptosis, invasion, and angiogenesis [4]. HDAC inhibitors have been shown to have pleiotropic effects on aberrant pathways in cancer cells, resulting in the induction of apoptosis and the inhibition of cell proliferation [3, 5]. Vorinostat, an inhibitor of class I, II, and IV HDACs, and romidepsin, an inhibitor of class I HDACs, received regulatory approval for the treatment of cutaneous T-cell lymphoma in 2006 and 2009, respectively [6, 7].

SB939 (chemical name: (2E)-3-[2-butyl-1-[2-(diethylamino)ethyl]-1H-benzimidazol-5-yl]-N-hydroxy-acrylamide hydrochloride) is a novel hydroxamate-based small-molecule inhibitor of class I, II, and IV HDACs. It is potent in its activity, having K_{i} values of 16–48 nM [with the exception of HDAC6 (247 nM)], and it is also selective. In particular, it does not inhibit [3H]-dofetilide binding to the human Ether-à-go-go Related Gene potassium channel [8].

In preclinical in vivo studies, orally administered SB939 demonstrated dose-dependent antitumor activity against a variety of experimental solid tumor models and was found to selectively accumulate in tumor tissue, as evidenced by concentrations that were 10-fold higher than those in plasma, liver, kidney, and lung tissue [9]. Repeated oral dosing studies showed it had a good safety profile in animals. The favorable
pharmacological properties of SB939 including high aqueous solubility, tissue permeability, and no major interaction with cytochrome P-450 isoenzymes, which indicate best-in-class potential, prompted the present phase 1 trial. This study evaluated the safety, tolerability, and pharmacokinetics (PKs) of SB939 when administered orally once a day, every other day, 3 days a week for 3 consecutive weeks in a 28-day cycle in patients with advanced refractory solid tumors, and evaluated histone acetylation in peripheral blood mononuclear cells (PBMCs) as a pharmacodynamic (PD) target efficacy biomarker. This schedule was chosen based on preclinical data that demonstrated good efficacy and safety profile.

patients and methods

patient eligibility

Eligible patients were those who had histologically or cytologically confirmed locally advanced or metastatic solid tumors that were either refractory to standard therapy or for which conventional therapy was not reliably effective. Other inclusion criteria included the following: the presence of disease measurable by computed tomography (CT) or magnetic resonance imaging; age ≥18 years; adequate end-organ function, defined as a neutrophil count ≥1.5 × 10^9/l, a platelet count ≥100 × 10^9/l, hemoglobin level ≥9 g/dl, total bilirubin level ≤1.5 × upper limit of normal (ULN); aspartate aminotransferase and alanine aminotransferase levels ≤2.5 × ULN (<5 × ULN in the presence of documented liver metastases); a serum creatinine level ≤1.5 × ULN or a calculated creatinine clearance ≥60 ml/min (Cockcroft–Gault formula); an Eastern Cooperative Oncology Group performance status of two or less; and a life expectancy of at least 3 months. All patients provided written informed consent. Patients were excluded from participation if they had experienced a significant cardiac event within the previous year; had a prolonged QTc interval on baseline electrocardiography; had brain metastasis, malabsorption, or human immunodeficiency virus infection; were taking concomitant valproic acid or another HDAC inhibitor; or were pregnant or breast-feeding.

study design

This study was an open-label phase I trial conducted at the National University Hospital and National Cancer Centre, Singapore. The study was approved by the domain-specific review boards of the participating institutions and the Health Services Authority, Singapore.

Patients received SB939 every other day, 3 days a week, for 3 consecutive weeks in a 28-day cycle. On dosing days, the drug was given orally in the morning in the fasted state with 250 ml of water. The starting dose of 10 mg three times a week was calculated based on the recommendation of one-sixth of the highest non-severely toxic dose in the dog (most sensitive species), applying allometric scaling to a human with a body surface area of 1.7 m² to yield a dose of 17 mg/day and adding an extra margin of safety. The dose for each successive dose level was based on the treatment-related adverse events observed during the first cycle of treatment in the preceding dose level.

Toxicity was graded according to National Cancer Institute—Common Terminology Criteria for Adverse Events version 3.0. Dose-limiting toxicity (DLT) was defined as grade 4 neutropenia of ≥7 days’ duration or grade 3 neutropenia with fever, sepsis, or both; grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding; any treatment-related grade 3 or higher non-hematologic toxicity except for suboptimally controlled grade 3 nausea and vomiting; treatment delay of ≥2 weeks; or missing four or more doses within a cycle because of a treatment-related adverse event.

A minimum of three patients per dose cohort were evaluated at escalating doses of SB939. Scheduled dose cohorts included 20, 40, and 80 mg. At any dose level, the occurrence of a non-dose-limiting grade 2 or higher treatment-related toxicity would lead to restriction of further dose escalation to 10-mg steps. A cohort was expanded to six patients if a DLT occurred in one of three patients during the first cycle of treatment. If two or more patients of six in a cohort experienced a DLT within the first cycle, that dose would be defined as the maximum tolerated dose (MTD) and dose escalation would be stopped. The next dose level below the MTD would then be defined as the recommended dose for phase II studies and be expanded to a maximum of 10 patients to assess tolerability.

Patients were treated until tumor progression, failure to recover from a DLT within 2 weeks of the last dose, withdrawal of consent, or discontinuation at the treating physician’s discretion. Dose reduction to the next lower dose level was allowed for patients who experienced a DLT but were judged to be clinically and/or radiologically benefiting from continued treatment. Discontinuation of treatment was mandatory for patients who experienced a grade 3 or 4 prolongation of the QTc interval. Grade 3 or 4 platelet or neutrophil toxic effects required dose reduction upon recovery to grade 2 or less. Up to two dose reductions were allowed in each patient. No intrapatient dose escalations were permitted.

patient evaluation

Patient assessments included the following evaluations: physical examination; complete blood count; serum chemistry studies, including troponin T level; urinalysis; and serial electrocardiography including triplicate electrocardiographic readings obtained both before dosing and at the estimated time to peak concentration (Tmax) after dosing as QTc prolongation has been associated with similar-class HDAC inhibitors [5]. Baseline tumor imaging was carried out by helical CT scan and repeated after every two cycles. Responses were evaluated using the RECIST criteria 1.0. Patients were considered eligible for radiological response assessment after at least two cycles of treatment.

PK analysis of SB939

sample collection. Blood samples for PK analysis were collected in K2EDTA tubes before dosing and at post-dose hours 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24 ± 2, and 30 ± 2 on day 1 (dose 1) and day 15 (dose 7). The samples were centrifuged at 1120 g for 10 min at 4°C, and the supernatant was stored at −80°C until analysis.

SB939 assay method. The bioanalytical method used to measure SB939 concentration was carried out and validated at the MPI Research Inc., State College, PA (detailed method in supplemental data, available at Annals of Oncology online). The method employed a liquid chromatography–tandem mass spectrometry (LC/MS/MS) procedure, with EX-12, a chemical analogue, as the internal standard. The method was validated through the quantification range of 0.5–500 ng/ml.

calculation of PK parameters. PK parameters were calculated by a noncompartmental method using WinNonlin 4.0 software (Pharsight Corp., Mountain View, CA). Peak plasma concentration (Cmax) and Tmax were estimated from the plasma drug concentration–time curve. Area under the concentration–time curve extrapolated to infinity (AUC(0-∞)) was calculated by the log-linear trapezoidal method for the observed values, with extrapolation to infinity including at least three points on the terminal phase. The elimination half-life (t1/2) during the log-linear terminal phase, oral clearance (CL/F), and volume of distribution (V/F) were calculated.

PD studies

histone acetylation. Blood samples for assessment of histone H3 acetylation were collected in 8-ml BD Vacutainer™ CPT™ tubes before dosing (time 0) and post-dose hours 3 and 24 ± 2 on days 1 and 15 of cycle 1 (for
results

patient characteristics

Thirty-one patients (15 men, 16 women) with a variety of tumor types were enrolled in the trial (Table 1) from April 2007 to August 2008. More than half of the patients had undergone at least three previous treatment regimens. One patient withdrew consent before initiating treatment. Twenty-four patients were eligible for response evaluation; 6 patients discontinued before tumor reassessment because of disease progression (3 patients), withdrawal of consent (2 patients), or toxicity (1 patient). A total of 79 cycles of SB939 were administered to 30 patients, with a median treatment duration of 2 cycles (range, 1–12 cycles).

DLTs and adverse events

Patients were enrolled into one of five dose cohorts ranging up to 80 mg. DLTs were experienced at and above the 40-mg level and were limited to grade 3 severity (Table 2). The MTD was reached at 80 mg, where three of six patients experienced treatment-related grade 3 fatigue, troponin T elevation, and QTc prolongation, respectively. The patient who experienced troponin T elevation had metastatic endometrial carcinoma and was asymptomatic and without electrocardiogram abnormalities though recurrent grade 2 elevation of troponin T was observed upon reintroduction of SB939 at 40 mg. Transthoracic echocardiogram showed normal myocardial function. Serum levels of troponin T normalized after SB939 was withheld. Of the 10 patients at the 60-mg dose level, one patient experienced grade 3 hypokalemia, and another experienced grade 3 QTc prolongation, both in cycle 1; both events resolved on drug withdrawal.

QTc prolongation of grade ≥2 severity was the only treatment-related toxicity that led to study drug discontinuation. This DLT occurred in one patient treated at 60 mg and in another treated at 80 mg. In both patients, the QTc prolongation was asymptomatic and was not accompanied by troponin T elevation or myocardial dysfunction on transthoracic echocardiography. The QTc abnormalities resolved without sequelae upon discontinuation of SB939.

Fatigue, anorexia, nausea, and vomiting were the most common non-hematologic toxic effects seen at all dose levels. These events were usually of grade ≤2 severity and did not result in dehydration requiring parenteral fluids. The most common hematologic toxicity was thrombocytopenia and was observed at the 60- and 80-mg dose levels (Table 3). No treatment-related deaths occurred in this study. The relative dose intensity of SB939 delivered at 60-mg dose level was 63% (Table 3). At this dose cohort, 4 of 10 patients had missed three or more doses due to treatment-related adverse events.

Twenty-five patients were assessed for day 1 PK: 3 (10 mg), 3 (20 mg), 7 (40 mg), 6 (60 mg), and 6 (80 mg), and 19 for day 15 PK: 3 (10 mg), 3 (20 mg), 5 (40 mg), 4 (60 mg), and 4 (80 mg). PK parameters were not estimated in 5 and 11 patients on days 1 and 15, respectively, because of either limited number of sampling time points or significant deviations from the sampling schedule. Plasma disposition of SB939 was characterized by rapid absorption, with $T_{\text{max}}$ reached in 1–2 h, followed by biexponential decay (Figure 1). The mean $t_\text{½}$ and CL/F of SB939 were 7.2 ± 0.6 h and 53.0 ± 8.5 l/h, respectively. The PKs of SB939 on days 1 and 15 were similar, and there was
no significant accumulation on day 15. \( C_{\text{max}} \) and AUC (0–\( t \)) increased in proportion to dose over the range of doses studied, with no evidence of saturation of drug absorption (Figure 2). Plasma concentrations of SB939 reached above the concentration that causes 50% inhibition of growth for HDAC1 (10 ng/ml [9]) at all doses studied (Figure 1).

pharmacodynamics

PBMCs for the PD analysis were obtained from 30 patients. Ten of these 30 patients were not assessable on day 15 because of missing sample points. Three samples (two in the 80-mg cohort and one in the 60-mg cohort) were excluded from the analysis for technical reasons.

A dose-dependent increase in acetylated histone H3 (acH3) was observed after SB939 administration on days 1 and 15. The highest levels of acH3 were observed at the 3-h post-dose sampling point, though mean acH3 levels at each dose level remained at least twofold higher (range 2- to 195-fold) from baseline at the end of day 1. There was a positive correlation between dose and the maximum observed levels of acH3 on day 1 (3 or 24 h post-dose; \( r^2 = 0.906; P = 0.013; \) Figure 3). Maximum relative acH3 values on day 1 also positively correlated with \( C_{\text{max}} \) (\( r^2 = 0.798; P = 0.0413 \). In the 60-mg cohort, the increase in acH3 at hour 3 on days 1 and 15 was significant (\( P = 0.027 \) and consistent in all patients. Maximum acH3 levels were more than six times higher than baseline in two patients who experienced a minor response.

clinical efficacy

Of the 24 patients assessable for response, stable disease was seen in 5 patients (21%), of whom four achieved disease stabilization for >6 months. No complete or partial responses were observed in this study. The median number of cycles administered for patients who achieved stable disease was 6 (range 3–12). A patient with follicular thyroid cancer who was treated at the 80-mg dose level completed 12 cycles and achieved disease stabilization for 331 days. Prolonged disease stabilization was also seen at the 60-mg dose level in one patient with heavily pretreated metastatic neuroblastoma and in one patient with advanced breast cancer (334 and 167 days, respectively). The patient with breast cancer had previously received goserelin and tamoxifen and five regimens of conventional chemotherapy. Before SB939 treatment, her disease was progressing rapidly. The patient with metastatic neuroblastoma had a minor response, with a maximum decrease in tumor size of 18.4%. At the 40-mg dose level, one patient with hepatocellular carcinoma who had progressed on sorafenib experienced stable disease for 164 days.

discussion

SB939 was selected for clinical development on the basis of its very favorable preclinical pharmacological properties and activity against a broad spectrum of cancer cell lines [9].

The efficacy data from preclinical studies [9] supported two dosing regimens that are being pursued clinically: thrice weekly for 3 weeks every 28 days and 5 days every fortnight every 28 days. The current study is a first-in-human trial of SB939 using the thrice-weekly regimen. Our results indicate that the MTD of SB939 using this regimen is 80 mg/day and that the recommended dose for phase II studies is 60 mg/day.

Table 3. Adverse events (AEs) related* to SB939 treatment that occurred with a frequency of ≥5% (counted by the highest grade per event per patient), graded according to National Cancer Institute—Common Terminology Criteria for Adverse Events (NCI–CTCAE) version 3.0.

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<td>5</td>
<td>8</td>
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<td>99</td>
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Hematologic

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<th>4</th>
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<th>2</th>
<th>3</th>
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</table>

aPossibly, probably, or definitely related to treatment.
PK and PD analysis showed dose-dependent increase in both exposure and the target efficacy biomarker (acH3 in PBMCs), with no accumulation after repeated dosing. The plasma $t_{1/2}$ of SB939, which ranged from 7 to 11 h, was shorter than that of panobinostat [10], similar to that of mocetinostat [11], and longer than that of either vorinostat or belinostat, which falls in the range of 1–2 h [12, 13]. Consistent with the preclinical observation of high tumor distribution [9], SB939 had a large volume of distribution at all dose levels in this study. Interindividual variability of CL/F was relatively low for an orally administered agent.

In preclinical testing, SB939 concentrations at and above 0.125 mM (44.81 ng/ml) induced acH3 in HCT-116 tumor cells [9]. These concentrations were achieved in the plasma of patients treated at $\geq 20$ mg/day (Table 4). AcH3 levels in PBMCs increased with dose, demonstrating a dose-dependent PD effect of SB939 in a surrogate tissue. Dose dependency of the PD response has not been clearly demonstrated in clinical trials with panobinostat, vorinostat, or belinostat [12, 14, 15]. Although a dose-dependent increase in inhibition of HDAC enzymatic activity in PBMCs has been shown in a phase I trial with mocetinostat, the effect on acH3 was not dose dependent [11]. This finding may be due to the high interpatient variability in oral absorption and the need for coadministration of acidic beverages to improve absorption [11]. In the 60-mg dose cohort, acH3 levels were consistently elevated in all patients, demonstrating strong target inhibition and supporting the selection of this dose for phase II trials. Interestingly, two of the patients treated with SB939 who experienced prolonged disease stabilization showed sustained elevation of acH3 levels after 15 days of repeated dosing. Our sample size precludes any statistical confidence in this finding, but it warrants further investigation in a larger patient population in future trials.

Adverse events related to SB939 were generally mild to moderate in severity and easily managed. The toxic effects observed increased with dose and were similar to those associated with other HDAC inhibitors in development [11, 12, 14, 15]. DLTs included fatigue, hypokalemia, cardiac side-effects, and thrombocytopenia, which was the most common hematologic toxicity. Nausea, vomiting, and dysgeusia were common but, unlike the experience with vorinostat [16], did not lead to dehydration even though prophylactic antiemetics were not used. SB939 had no effect on creatinine with repeated cycles of treatment, and there were no episodes of
In summary, this phase I study in patients with refractory solid tumors has shown that SB939 can be safely administered for prolonged periods, has an excellent PK profile after oral dosing, and results in strong target inhibition in PBMCs, a surrogate for tumor tissue. These data support further efficacy studies of SB939 both as a single agent and in combination with standard therapies, and phase II studies are currently in progress.

funding

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disclosure

K.E., J.W., V.N.-D., and J.Z. are employees of S*BIO Pte Ltd. The other authors have declared no conflicts of interest.

references


Table 4. Pharmacokinetic parameters of SB939 obtained using noncompartmental analysis (mean ± standard deviation)

<table>
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<tr>
<td></td>
<td>V/F (l)</td>
<td>442 ± 102</td>
<td>616 ± 191</td>
<td>587 ± 218</td>
<td>584 ± 204</td>
<td>490 ± 318</td>
</tr>
<tr>
<td>Study day 15</td>
<td>n</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>1.0 ± 0.5</td>
<td>2.0 ± 1.0</td>
<td>1.3 ± 0.3</td>
<td>1.0 ± 0.4</td>
<td>1.6 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>40 ± 13</td>
<td>70 ± 36</td>
<td>150 ± 82</td>
<td>215 ± 48</td>
<td>361 ± 230</td>
</tr>
<tr>
<td></td>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng h/ml)</td>
<td>283 ± 50</td>
<td>468 ± 125</td>
<td>722 ± 321</td>
<td>1226 ± 438</td>
<td>2244 ± 1281</td>
</tr>
<tr>
<td></td>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>9.4 ± 1.4</td>
<td>7.6 ± 1.9</td>
<td>7.1 ± 1.3</td>
<td>7.1 ± 0.8</td>
<td>8.1 ± 2.1</td>
</tr>
<tr>
<td></td>
<td>CL/F (l/h)</td>
<td>36 ± 7</td>
<td>45 ± 13</td>
<td>63 ± 22</td>
<td>53 ± 16</td>
<td>45 ± 23</td>
</tr>
<tr>
<td></td>
<td>V/F (l)</td>
<td>481 ± 20</td>
<td>471 ± 51</td>
<td>634 ± 200</td>
<td>542 ± 180</td>
<td>564 ± 385</td>
</tr>
</tbody>
</table>

T<sub>max</sub>, time to peak concentration; C<sub>max</sub>, peak plasma concentration; AUC<sub>0-∞</sub>, area under the concentration–time curve extrapolated to infinity; t<sub>1/2</sub>, elimination half-life; CL/F, oral clearance; V/F, volume of distribution.

thromboembolism, which have been reported for vorinostat [16]. As with other HDAC inhibitors, fatigue was gradual and peaked toward the third and fourth week of each cycle. Cardiac-related side-effects included grade 3 QTc prolongation and asymptomatic elevation of T<sub>max</sub> and both were reversible on drug withdrawal. QTc prolongation appears to be a class effect for HDAC inhibitors, the actual incidence and severity of which is dependent on dose and schedule used for each HDAC inhibitor. Although QTc prolongation poses a risk for malignant cardiac arrhythmia with torsade de points and sudden cardiac death, it is recognized that, with few exceptions, the QT abnormalities observed in HDAC inhibitor clinical trials have not translated into symptomatic or clinically meaningful events [17]. Although no partial responses were seen, prolonged non-progression of breast cancer, follicular thyroid carcinoma, neuroblastoma, and hepatocellular carcinoma were promising observations. Neuroblastoma cell lines are reported to be pretreated neuroblastoma. These results suggest potential antitumor activity of SB939 in this disease. Recently, HDAC inhibitors have been shown to reverse therapy resistance in endocrine-related cancers like breast cancer and thyroid cancer via up-regulation of hormone receptors and sodium iodide receptors, respectively [19–22]. These findings suggest promising directions for development of this drug class in combination with other therapies. Indeed, this potential has been reported with the combination of vorinostat, paclitaxel, and carboplatin in lung cancer [23]. An anti-angiogenic effect is one of several putative mechanisms for the antitumor efficacy of HDAC inhibition [24]. The possibility of combining HDAC inhibitors with anti-vascular endothelial growth factor receptor agents may be worth considering given the lack of overlapping DLTs.