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

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TREATMENT-RELATED SERIOUS ADVERSE EVENTS SAFETY SUMMARY

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 (Mol-01) and B-cell lymphoma (Ramos) as well as in models of solid tumors.

It is being 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 IC50 of 0.1–1.3 μM.

Lymphocytes and monocytes of hematologic 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 2 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 toxic x-factors in PSMA as well as other biomarkers

STUDY DESIGN

Phase 1, multicenter, open-label, escalating dose cohort study

Subjects were treated at one dose level for a minimum of 2 months (3 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 DISPOSITION (as of November 2010)

N = 44

Evaluable for safety (received at least one dose) = 44

Evaluable for response = 44

Median time on study drug, days (range) = 48 (2–307)

Patients on study drug > 3 months = 11

Dose-limiting treatment prior to Cycle 1 = 31

Diabetes = 9

Inadequate performance status = 5

Non-responsive = 4

Death = 3

DOSE-LIMITING TOXICITIES

DLT criteria must have occurred during Cycle 1:

• Treatment-related non-hematologic toxicity Grade 3/4 (including Grade 3 anemia occurring with suboptimal anti-emetic therapy) (proven in subjects with malignant peripheral nerve sheath tumor (MPNST))

• Neutropenia Grade 4 lasting 7 or more days or neutropenia Grade 4 with fever and/or infection

• Thrombocytopenia Grade 4 or platelet count < 20,000/mm3

• Dose delay > 2 or < 4 missed doses because of a treatment-related AEs or an abnormality

• 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 (52%), nausea/vomiting (46%), anorexia (23%), diarrhea (17%), and thrombocytopenia (16%)

• The most common treatment-related Grade 3/4 toxicities were neutropenia (17%) and fatigue (11%)

• Dose-limiting toxicities consisted of asymptomatic QT prolongation (2 subjects), a possible class effect of HDAC inhibitors, and worsening hypotension

• The MTD as defined was not reached.

• 100 mg was determined to be the recommended dose for Phase 2.

PHARMACOKINETIC ANALYSIS

• SB939 showed rapid absorption and bispemiphal disposition

• The corrected QT interval (QTc) was normal

CONFLICT OF INTEREST STATEMENT

H. J. Zhu and K. Ethirajulu are employees of S*BIO Pte Ltd. All other authors disclose no conflict of interest.

REFERENCES

(Cont.)