1.0 SCIENTIFIC ABSTRACT

1.1 Background

SB623 cells are adult human bone marrow-derived neuroprogenitor cells and are being developed as an allogeneic cell therapy for chronic, stable stroke and other neurodegenerative conditions. SB623 cells are generated under GMP conditions by the transient transfection of bone marrow stromal cells (donated from normal healthy adults) with a plasmid encoding the human Notch-1 intracellular domain. Implanted SB623 cells are expected to integrate into the area of the stroke-damaged brain tissue and lead to regeneration of functional neurons, restoring patient motor function.

A number of preclinical studies have been performed to demonstrate the safety and efficacy of SB623 in validated animal models. The most relevant to this proposal is a surgically-induced stroke in rats caused by the transient occlusion of the middle cerebral artery (the MCAo model). Rats given an MCAo stroke were treated one month after surgery by stereotactic implantation of SB623 cells. Using an elevated body swing test for whole body motor function evaluation, it was observed that the rotational bias was reduced from >90% to 60% within 14 days after implant. From this same study a more integrated neurological evaluation called the Bederson Score was also performed, involving a 4 component evaluation of stroke disability involving spontaneous ipsilateral circling, contralateral limb retraction, beam walking, and bilateral forepaw grasp. Within 7 days the animals had experienced 30% improvement in their Bederson scores which then further improved to >40% and stabilized after 14 days. These effects persisted for 28 days, the designed end of the study.

Two animal safety studies have been conducted. Stereotactic intrastriatal implantation of 0.5 million cells into athymic nude rats with planned follow-up of 12 months has shown no cell-related adverse findings through 6 months, with endpoints of laboratory parameters, gross observations, gross necropsy, and histologic examination.[1] Similarly, stereotactic intrastriatal implantation of 10 million cells into immunosuppressed Cynomolgus monkeys with planned follow-up of 6 months has shown no cell-related findings through 3 months.[2]

SB623 cells may reverse neurodegeneration through several mechanisms. *In vitro* studies have shown that SB623 cells differentiate into cells with neuronal morphology with expression of neuron-specific markers such as tyrosine hydroxylase and choline acetyltransferase, thus resembling dopaminergic and cholinergic neurons, respectively. Similarly, SB623 cells may differentiate in the brain after implantation and may replace damaged or dead neurons. Another possible mechanism may be that SB623 cells provide trophic support for dysfunctional host neurons. Analysis of SB623-conditioned medium has revealed the secretion of several factors known to be neuroprotective. Thus, both direct and indirect mechanisms may contribute to the overall beneficial effect of SB623 in reversing motor function loss due to stroke.

1.2 Study Design

SanBio is proposing a Phase 1/2a, single-arm, dose-escalation, 24-month safety study of 18 patients (6 patients per dose level) with fixed neurologic deficits following ischemic stroke. The Phase 1/2a study will focus on establishing the safety of the SB623 bone marrow derived

neuroprogenitor cell implants for the treatment of fixed neurological deficits resulting from chronic ischemic stroke. An independent Data Safety Monitoring Board (DSMB) will monitor patient safety and provide advice on the trial operations. Possible efficacy will also be determined by standard scoring assessments and radiologic measures.