SANBIO INCORPORATED
CLINICAL PROTOCOL

TITLE: A Phase 1/2A Study of the Safety and Efficacy of Modified Stromal Cells (SB623) in Patients with Stable Ischemic Stroke

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Investigator Statement

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1.0 PROTOCOL SYNOPSIS

Protocol #:	SB-STR01
Title:	A Phase 1/2A Study of the Safety and Efficacy of Modified Stromal Cells (SB623) in Patients with Stable Ischemic Stroke
Study Objectives:	Primary: To evaluate the safety and tolerability of intracranial administration of SB623 cells. Safety will be determined during 2 years post-implant. Secondary: To evaluate clinical and radiographic response to 3 dose levels of intracranial administration of SB623 cells. The major efficacy endpoints will be determined at 6 months; measures will also be at 1, 2, 3, 4, 9, 12, and 24 months.
Background and Rationale	SB623 cells are adult bone-marrow-derived cells that have been transiently transfected with a plasmid construct encoding the intracellular domain of human Notch-1. SB623 cells secrete factors that protect neurons in models of ischemic insult. In a rat occlusion model of stroke to the middle cerebral artery region, implantation of SB623 into and around the area of the infarct resulted in improvement of neurological behavior. The safety of implanted SB623 cells was evaluated in a 6-month primate study and in 2 nude rat studies (4 mos. and 12 mos.). The primates were immunosuppressed with cyclosporine and the nude rats further immunosuppressed with an anti-NK cell antibody. There were no SB623-related clinical, laboratory, or histological abnormalities found. The stereotactic surgical delivery of cells to patients with stroke has been shown to have an acceptable safety profile in two prior clinical studies with another product. In addition, a retrospective study of over 2,650 patients undergoing stereotactic surgery during a 28-year period at one major clinic has shown a high degree of safety with the procedure. Finally, the European Stroke Scale (ESS), the Modified Rankin Score, the National Institute of Health Stroke Scale (NIHSS), the Fugl-Meyer scale for motor function, and a neurocognitive battery (*e.g.*, Rey Complex Figure Test), have been used and validated, at least for acute stroke. Fluorodeoxyglucose positron emission tomography (FDG-PET) imaging has shown that changes in metabolic activity relative to baseline in the infarct area and surrounding areas correlated with performance on the motor subscale of the ESS.
Study Design	This is an open-label safety study of stereotactic, intracranial injection of SB623 cells in patients with hemiparesis from stable ischemic stroke who have remained stable during the prior 3 weeks (based on NIHSS assessments at weeks -3 and -1). While primarily a safety study, efficacy parameters will also be evaluated. Three cohorts will receive escalating single doses of SB623, which are to be stereotactically implanted into grey or white matter sites adjacent to the infarct region. One burr-hole craniostomy will be created, and cells implanted using 3 needle tracks with 5 deposits for each track at varying depths around the damaged area. Cell

	implantation will be standardized as to volume (20 µL/deposit) and rate (10 µL/min), with spacing between each implant of approximately 5-6 mm. Each deposit is expected to take approximately 2-3 minutes, with each needle track being completed within 15 minutes. Each cohort will consist of 6 subjects defined by an increasing total number of cells implanted. Safety will be monitored by the Investigator, Principal Monitor, Medical Monitor, and an external Data Safety Monitoring Board. For the first cohort, a single patient will first be dosed, then evaluated over a 2 week period for safety prior to dosing the next member of the cohort. This 2-week interval will continue between each of the remaining members of this cohort. If the safety profile is acceptable for a cohort, and after review by the DSMB, the first patient in each subsequent cohort will be dosed, beginning 4 weeks after dosing of the last patient of the prior cohort. For the second and third patients in each of the subsequent cohorts, there will be an interval of 2 weeks after the prior patients prior to further enrollment. Safety will be monitored by clinical symptoms, laboratory findings, and MRI brain imaging. Two or more serious adverse events will trigger a review by the DSMB before continuing enrollment. Possible efficacy will be determined based on changes in the clinical measures of stroke through standardized assessments and on FDG-PET brain imaging. A dose-limiting toxicity will be defined as any grade 3 or 4 event which is at least possibly related to study product or administration procedure If the first patient in a cohort has a dose-limiting toxicity attributable to the SB623 cells, then no further patients will be dosed in that cohort until a comprehensive evaluation has been conducted. If 2 of 6 patients in a cohort have a dose-limiting toxicity attributable to the SB623 cells, then no further patients will be dosed in that or higher-dose cohorts. Each dose-limiting-toxicity will be evaluated by the DSMB. The DSMB shall be the final arbitrator for attributions.
Patient Population	Adult patients with hemiparesis from stable ischemic stroke. Stable stroke will be defined as 6-60 mos. post stroke with motor neurological deficit, post-physical therapy, and with no more than ±1 point change in clinical stroke evaluation (using NIHSS) in the 3 weeks prior to study enrollment. The interval of 6-60 months for this patient population is based on a number of studies that have shown that over 90% of ischemic stroke patients are stable by 90 days post-stroke. The upper limit of 36 mos. was chosen to allow for the possibility of some brain tissue plasticity remaining, while mainly to increase the potential patient population.
Statistical Considerations	Based on the animal data, no dose-limiting toxicity is expected. However, if the true rate of toxicity is 40%, a sample size of 6 patients per cohort would result in a < 5% chance of missing a dose-limiting toxicity. A pooled analysis of changes from Baseline for all patients for each of the efficacy parameters will be conducted. In addition, a possible dose-response will be evaluated.
No. of Patients	18 Evaluable

No. of Study Sites	Up to 8
Inclusion Criteria	• Age 18-75 years • Documented history of completed ischemic stroke in subcortical region of MCA or lenticulostriate artery with or without cortical involvement, with correlated findings preferably by MRI or by CT if MRI is contraindicated • Between 6 and 60 months post-stroke, and having a motor neurological deficit • No significant further improvement with physical therapy/rehabilitation (confirmed by no change in NIHSS greater than ±1 within three weeks prior to enrollment) • Modified Rankin Score of 3 or 4 • NIH Stroke score of >7 • Two evaluations during prior 3 weeks with no more than ±1 point change in clinical evaluation using the NIH Stroke Scale • Able and willing to undergo computed tomography (CT), magnetic resonance imaging (MRI), and positron-emission tomography (PET) scans of the head • Agree that use of antiplatelet, anti-coagulant, or non-steroidal anti-inflammatory drugs to be determined by the local medical staff and in accordance with the ACCP 2012 guideline "Perioperative Management of Antithrombotic Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th Edition: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines", if applicable[1], provided that no antiplatelet, anti-coagulant, or non-steroidal anti-inflammatory drugs are to be restarted post surgery until after the Day 8 MRI is read and are determined to be safe to re-start • Normal emotional status; *i.e.*, no disabling psychological deficits • Ability of patient or legal authorized representative to understand and sign an Informed Consent
Exclusion Criteria	• History of more than 1 symptomatic stroke • History or presence of any other major neurological disease • Cerebral infarct size >100 cm^3 measured by MRI • Myocardial infarction within prior 6 mos. • Known presence of any malignancy except squamous or basal cell carcinoma of the skin • History of CNS malignancy • History of seizures or current use of antiepileptic medication • Uncontrolled systemic illness, including, but not limited to: hypertension (systolic >150 mm Hg or diastolic >95 mm Hg); diabetes; renal, hepatic, or cardiac failure • Uncontrolled psychiatric illness, including depression (Hamilton Score of >14) • Total bilirubin >1.5 mg/dL • Serum creatinine >1.5 mg/dL

	• Hemoglobin <10.0 g/dL • Absolute neutrophil count <2000 /mm^3 • Lymphocytes <800 /mm^3 • Platelet count <100,000/mm^3 • Liver disease supported by AST (SGOT) or ALT (SGPT) ≥2.5 x institutional upper limit of normal • Serum calcium >11.5 mg/dl • International Normalized Ratio of Prothrombin Time (INR) >1.2 • Signs and symptoms of intracranial herniation or increased intracranial pressure • Acute intracranial hemorrhage • Use of neuroleptic drugs • Unexplained abnormal preoperative test values (blood tests, electrocardiogram [ECG], chest X-ray); patients with electrocardiographic evidence to suggest a recent myocardial infarction, major dysrhythmia, x-ray evidence of infection, atrial fibrillation, or congestive heart failure will be excluded • Participation in any other investigational trial within 4 weeks of initial screening and within 7 weeks of study entry • Botulinum toxin injection, phenol injection, intrathecal baclofen, or any other interventional treatments for spasticity (except bracing and splinting) within the previous 3 mos. • Ongoing use of herbal or other non-traditional drugs • Ongoing drug or alcohol abuse • Contraindications to head CT, MRI, or PET • Pregnant or lactating • Female patients of childbearing potential unwilling to use an adequate birth control method during the first 6 months of the study • Presence of serum antibodies to donor SB623 cells with a Luminex value of >1000 MFI (Maximum Fluorescence Intensity): HLA Class I (HLA-A*23:PWMV, HLA-A*68:CGBR; HLA-B*45:FJH, HLA-B*53:KJW; or HLA-Bw4, HLA-Bw6; HLA-Cw*04:SSWB, HLA-Cw*16:01); or Class II (HLA-DRB1 *13:NGUB, HLA-DRB1 *16:02; HLA-DQB1*05:CHZY, HLA-DQB1*05:BK; HLA-DQA1*01:DVB, HLA-DQA1*X, HLA-DRB3,4,5: 3*03:01, HLA-DRB3,4,5: 5*02:02) • Any other condition or situation that the investigator believes may interfere with the safety of the subject or the intent and conduct of the study
Dosage, Mode of Administration, and Treatment Duration	All dosages of cells to be administered stereotactically through one burr-hole craniostomy within and adjacent to the infarct using 3 needle tracks and 5 cell deposits per track at varying depths (20 µL each). Cohort 1: 2.5 X 10^6 SB623 Cells (8.3 X 10^6 cells/mL) Cohort 2: 5.0 X 10^6 SB623 Cells (17 X 10^6 cells/mL) Cohort 3: 10 X 10^6 SB623 Cells (33 X 10^6 cells/mL)

Duration of Patient Study Participation	Two years (except if there is an unresolved Grade 2 adverse event at least possibly related to the therapy, in which case the patient will be followed until resolved or reduced to Grade 1).
Cell Storage Conditions and Reconstitution	SB623 cells will be kept frozen in vapor phase liquid nitrogen at study sites within the shipping container until ready for use, then thawed, washed, and re-suspended at one of 3 different concentrations in Plasma-Lyte A® as summarized above.
Efficacy Parameters	• Clinical improvement of stroke symptoms using the European Stroke Scale, the NIH Stroke Scale, and the Modified Rankin Scale, improvement in motor functions using the Fugl-Meyer scale, and improvement in cognitive status using a test battery (including Rey Complex Figure Test) • Increase in fluorodeoxyglucose (FDG) uptake measured by positron emission tomography (PET)
Safety Parameters	• SB623- and surgical-related adverse events using WHO toxicity criteria • Adverse changes imaged by head MRI (edema, adverse anatomical changes) • Serious adverse events (SAEs) using WHO toxicity criteria • Serum chemistry and hematology
Other Laboratory Parameters	• Serum levels of antibodies to SB623 cells and PBMC function assay • Development of serum antibodies to donor SB623 cells: HLA Class I (HLA-A*23:PWMV, HLA-A*68:CGBR; HLA-B*45:FJH, HLA-B*53:KJW; or HLA-Bw4, HLA-Bw6; HLA-Cw*04:SSWB, HLA-Cw*16:01); or Class II (HLA-DRB1 *13:NGUB, HLA-DRB1 *16:02; HLA-DQB1*05:CHZY, HLA-DQB1*05:BK; HLA-DQA1*01:DVB, HLA-DQA1*X, HLA-DRB3,4,5: 3*03:01, HLA-DRB3,4,5: 5*02:02)

2.0 BACKGROUND

2.1 Medical Need

Stroke is the third leading cause of death in the United States, Europe, and most countries in the world.[2,3,4,5] In 2007, nearly 700,000 new or recurrent strokes and 160,000 stroke-related deaths were expected to occur in the United States.[6,7] In addition, magnetic resonance imaging (MRI) studies reveal that nearly 22 million asymptomatic strokes occur every year.[8] Stroke is also a major cause of prolonged neurologic disability in adults,[3,4,6,8,9] with an annual economic burden of over $62 billion in the United States.[10] In addition to the main risk factor of hypertension, diabetes is also recognized as a significant risk factor.[11] Thus, incidences of stroke-related deaths and disability are expected to rise even higher as the population ages,[2,4,5,12,13] and as the incidence of diabetes increases.[14]

2.2 Treatment of Ischemic Stroke

2.2.1 Current Therapies

For acute ischemic stroke, immediate post-stroke interventions focus on life support through respiratory and cardiac control of blood pressure, monitoring oxygen saturation and blood glucose level, prevention of metabolic disturbances, maintenance of organ function, and management of elevated intracranial pressure.[15] The only approved therapies in the U.S. are thrombolytic agents, to be given within 3 hrs. of onset of the stroke. It has been estimated that less than 5% of acute ischemic stroke patients receive this therapy, probably due to the stringent criteria for thrombolytic intervention, the patient arrival beyond the 3-hour window, and lack of adequate facilities at many hospitals.[16] As the stroke fully develops, and the patient stabilizes, some regimen of physical therapy is almost universally applied.

2.2.2 Time Course for Stable Stroke

Acute ischemic stroke is generally accepted to be defined as up to several days, if not hours. Longitudinal studies on rates of improvement after ischemic stroke have shown that 90% of patients with ischemic stroke achieve no further improvement after about 90 days.[17] This time period was found to be independent of degree of initial severity regardless of methods used to assess by most investigators,[17,18,19] while others found that severe and very severe cases continued to have slight improvement for 2-3 weeks more using a different method of assessment.[20]

2.2.3 Experimental Cellular Therapies

For the stable stroke patient, no proven therapies exist to reverse the damage and improve overall motor or cognitive function. As reviewed recently, a variety of cellular therapies have been examined.[21,22,23] Clinical trials with these agents have so far been limited, with only three trials conducted and reported to date, with only two having used human cells.

Fetal cells from the porcine lateral ganglionic eminence which had been shown to improve deficits in an animal model of Huntington's disease,[24,25] and in an animal model of middle-cerebral artery occlusion[26] were studied in a Phase 1 clinical trial. Five patients with chronic, stable, moderate-sized basal ganglia infarcts received intrastriatal implantation of the cells. One of the patients developed a cortical vein occlusion, and the study was terminated by the Food and Drug Administration. Attribution of the adverse event has not been clarified. None of the patients showed improvement on the Modified Rankin Scale.[23]

Cultured human neurons derived from an embryonal carcinoma cell line that was isolated from a teratocarcinoma (LBS-Neurons) which had been shown to improve deficits in an animal model of middle-cerebral artery occlusion[27] were studied in an open-label Phase 1 clinical trial.[28,] Initially, 4 patients with stable stroke received stereotactic implants 2 million cells in one needle track into the area of infarction, divided into 3 implants with 20 µL per implant.. Subsequently, 8 additional patients were randomized to receive either single-pass (2 million cells in 3 implants) or 3-pass (6 million cells in 9 implants) injections into the area of infarction. All patients also received cyclosporine A orally. The outcomes were that the procedures and injections were well tolerated with a mean improvement in all patients by the European Stroke Score (ESS) that was statistically significant, and with an improvement in FDG-PET scans in half of the patients at 6 months.

Based on the encouraging results from that Phase 1 study, an open-label, observer-blinded Phase 2 study was conducted with LBS-Neurons in 18 patients who were randomized between surgery with 5 or 10 million cells implanted (25 implantation sites) plus rehabilitation (14 patients), or rehabilitation alone (4 patients), with all surgical patients also receiving cyclosporine A orally.[29] The patient mix was approximately an equal number with ischemic or hemorrhagic stroke. The outcomes were that both the procedure and the cell implants were again well tolerated. There was no statistically-significant improvement in the ESS between groups, although some improvements were found when patients were analyzed as their own controls. Some cognitive improvements were also noted. Finally, there were statistically-significant improvements in some of the Fugl-Meyer assessments, but not on overall motor function.

2.2.4 Stereotactic Surgery

In addition to the two studies referred to above with LBS Neurons, a retrospective study of over 2,650 patients who received stereotactic surgery over a 28-year period at one major clinic found an incidence of surgery-related complications to be <1%, establishing the high degree of safety for this procedure. Complications reported included a need for a craniotomy for hematoma evacuation (0.36%), perioperative seizures (0.36%), burr hole infections (0.08%), and death (0.08%).[30]

2.3 Methods to Evaluate Severity of Stroke

No one method has been shown to be adequately encompassing to evaluate the severity of stroke, since a constellation of symptoms is usually present. Accordingly, neurologists use several methods to score neurological deficits, including standardized stroke scales such as the European Stroke Scale (ESS),[31] the National Institutes of Health Stroke Scale (NIHSS),[32,33] the Modified Rankin Scale (MRS),[34,35] the Hemispheric Stroke Scale (HSS),[36] the Fugl-Meyer scale for motor deficits,[37,38] and a battery of cognitive tests.[39] A variety of other tests have also been used.

2.4 Rationale for Use of SB623 cells in Stroke

2.4.1 Summary of SB623 Cells Properties

SB623 cells are human bone marrow-derived 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 (MASC) with a plasmid encoding the human Notch-1 intracellular domain.[40] This

transfection is considered transient because the plasmid rapidly disappears with further expansion/passaging of the cells. Thus, the gene and its products which were initially detected at very low levels are not expected to be present at all after a short time post-implantation.

Unlike the MASC cells used to produce SB623 cells, the product has limited potential to differentiate into bone or adipose cells.

2.4.2 Summary of Notch-1 Gene Properties

Notch-1 is involved in the regulation of the development process in many species, including humans. Notch is a heterodimeric transmembrane receptor. Its natural ligands (Serrate, Jagged, Delta) are also integral membrane proteins, revealing a cell-cell or juxtacrine role for Notch. Once stimulated by a ligand, Notch is proteolytically cleaved releasing the Notch IntraCellular Domain (NICD) from the plasma membrane. Once released, the NICD migrates to the nucleus where it plays the role of an activating transcription factor for a number of genes.

3.0 Overall Experience with Investigational Product

This section includes a brief summary of preclinical data available on SB623. More detailed information can be found in the Investigator's Drug Brochure for SB623 cells.

3.1 Study Agent

SB623 cells are bone-marrow-derived stromal cells that have been transiently transfected with the intercellular domain of the human Notch-1 gene.

3.2 Preclinical Pharmacology

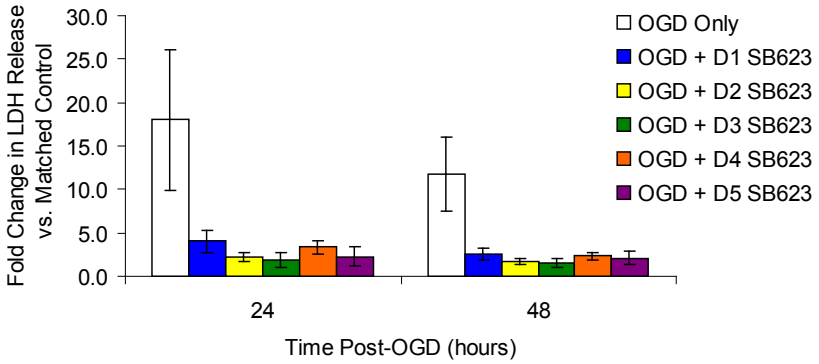
3.2.1 In Vitro

The *in vitro* characterization of SB623 cells has included 8 basic areas: fate of SB623 cells, protection of primary neurons from Oxygen Glucose Deprivation, the secretion of neurotrophic factors, Notch-1 signal transduction, epigenetic changes, osteo- and adipogenesis, and anti-inflammatory properties of SB623. See the Investigator's Drug Brochure for details on these studies.

3.2.1.1 Protection from Oxygen/Glucose Deprivation

Figure 1 shows the effects of SB623 co-culture on hippocampal slices. Similar protection was observed using SB623 conditioned medium (not shown) Taken together, these results strongly suggest that SB623 cells secrete soluble factors that can protect neurons.

Figure 1 SB623 co-culture protects primary rat hippocampal slices from OGD



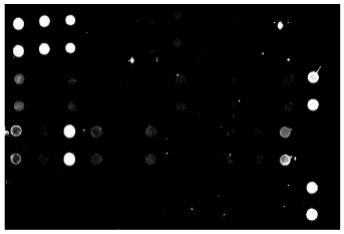
Data are expressed as fold change over untreated controls. Measurements were taken at 24 and 48 hours post OGD. SB623 cells were produced from 5 different donors.

3.2.1.2 Trophic Factor Secretion

The starting material for SB623 is bone marrow aspirate, from which are isolated Marrow Adherent Stromal Cells (MASC) also known as Marrow Stromal Cells (MSC). These cells have been extensively studied and are known to secrete a wide variety of factors. Independent of MSCs, a variety of factors have been shown to be implicated in beneficial effects for cerebral ischemia. Figure 2 shows the list of cytokines that were investigated. The ones in blue are secreted by both SB623 and MSC. The ones underlined are secreted by SB623 in much higher concentrations compared to MSC.

Figure 2 Trophic Factors Released in Conditioned Medium

- Custom antibody array (RayBiotech)
- 30 cytokines



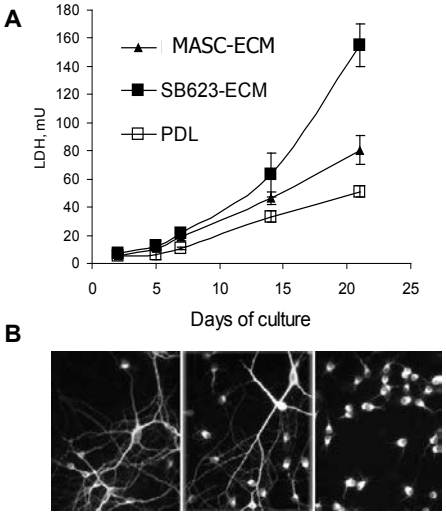
BDNF	HGF
BMP-4	IGF-I
BMP-6	IL-1α
BMP-7	IL-6
b-NGF	IL-8
CNTF	LIF
DKK-1	MCP-1
DKK-4	MMP-1
EGF	NT-3
Erythropoietin R	PDGF-AA
FGF-2	SDF-1
FGF-7	TGFα
GCSF	TGFβ
GDNF	TNFα
HB-EGF	VEGF

The right panel shows the results from a Ray Biotech antibody array. The list on the right show factors found in MASC and SB623 conditioned media (blue) and those preferentially produced by SB623 (underlined).

3.2.1.3 Extracellular Matrix Secretion

SB623 cells have been shown to secrete beneficial extracellular matrix in culture with rat neural cells, as measured by a increase in growth of intact cells. This is illustrated in Figure 3 below.

Figure 3 SB623 Cells Secrete Beneficial Extracellular Matrix



Panel A shows cell mass (as Lactate Dehydrogenase) vs. days in culture. Poly-D-lysine (PDL) serves as a control. Panel B show a photomicrograph from MASC. SB623 and PDL respectively.

In this experiment, culture of MSC or SB623 with poly-D lysine as control resulted in secretion of matrix. When rat neuronal cells, including glia, were allowed to grow on the matrices, the rate growth was much faster with SB623 matrix compared to MSC-matrix, as measure by the number of intact cells using concentration of LDH after lysing as a surrogate. As seen in B of the figure, both SB623 matrix and MSC matrix resulted in rat neurons Secretion of Matrix

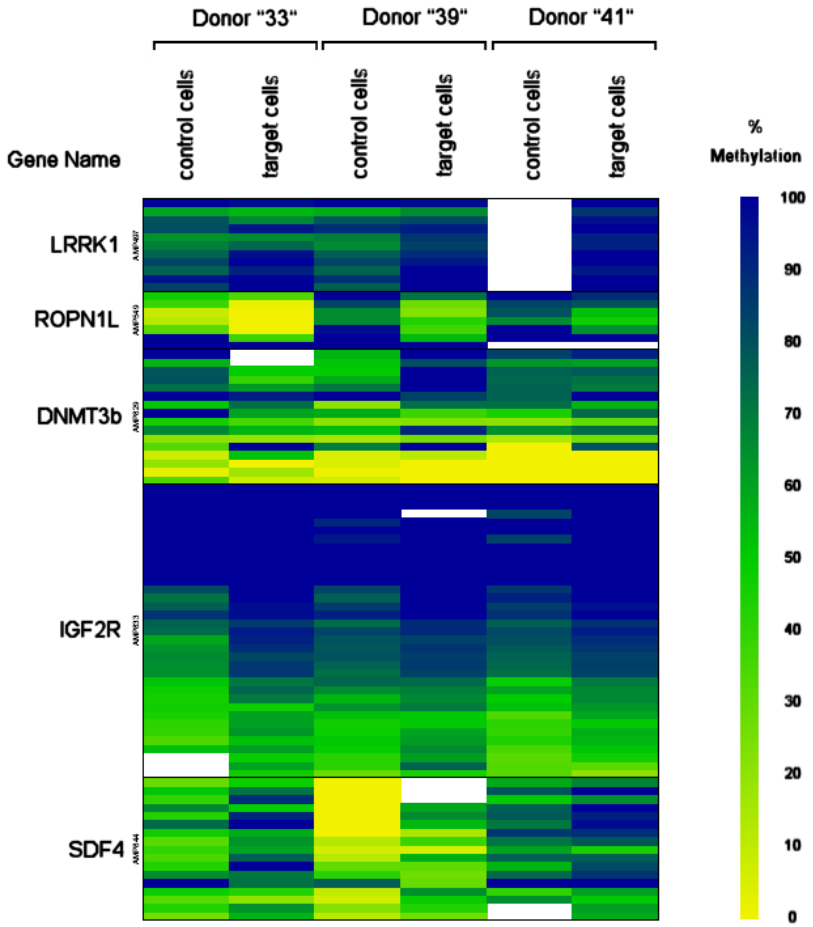
3.2.1.4 Epigenetic Changes

SB623 cells are produced by *transient* transfection of MASC cells. A stable phenotypic change in the absence of a change in the genomic sequence is defined as epigenetic. There are a wide variety of epigenetic marks that can specifically alter gene expression and alter cellular behavior. These include covalent modifications (acetylation, methylation, *etc.*) of the N-terminal "tails" of the histones, creating more or less densely packed chromatin and thereby altering the accessibility of RNA polymerase and other components of the transcriptional apparatus to their DNA targets. This is one of the basic mechanisms controlling gene expression. Another form of epigenetic control is accomplished by DNA methylation. The sequence CpG is underrepresented in the genome. There are enzymes that can methylate the 5 position of cytosine *de novo* and others that complete the methylation of hemi-methylated CpG/GpC basepairs, creating a heritable mark. There are high densities of

CpGs near the promoters of about half of the genes in the human genome. These CpG "islands" are typically in hypomethylated in undifferentiated cells. When the CpG island of a particular gene becomes hypermethylated, chromatin density increases and down-regulates the expression of that gene.

SB623 cells have an altered developmental potential when compared to the MASC source cell. We reasoned that the pattern of CpG methylation might be different in SB623 *vs*. MASC. In ongoing work with a contract research laboratory (Epiontis, GmbH, Berlin), we performed bisulfite sequencing on CpG islands associated with a collection of candidate genes. The results are shown in Figure 4.

Figure 4 CpG methylation status of 5 different genes for 3 donors



Each individual colored bar represents a PCR amplicon within a gene-associated CpG island. Multiple amplicons represent each gene. The sequence pre- and post-bisulfite conversion repeals the number of methyl-Cs present in the amplicon. The degree of methylation is indicated by color (yellow = completely unmethylated, blue = 100% methylated. White bars mean no sequence could be obtained. MASC (control) and SB623 (target) from three different donors were compared.

Figure 4 reveals that 4 of the 5 genes examined (LRKK1, ROPN1L, IGF2R and SDF4) are more methylated in SB623 than in MASC. One gene (DNMT3b) is less methylated in SB623 compared to MASC.

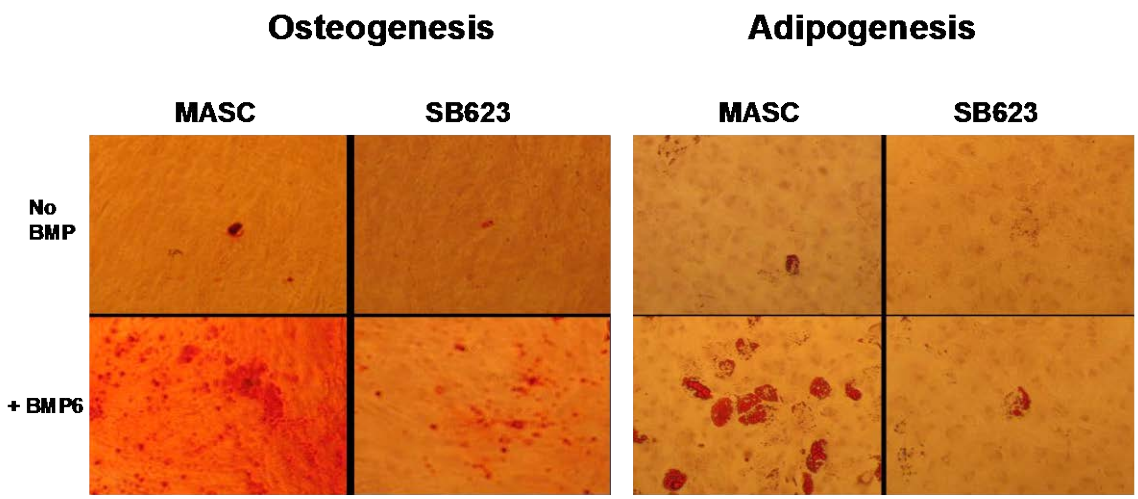
We are currently looking more globally at DNA methylation. If this pattern holds, (increase methylation in SB623) we can conclude that SB623 cells are more differentiated than MASC. This should also lead to candidate genes to help explain SB623 properties at a molecular level.

3.2.1.5 Effects on Osteogenesis and Adipogenesis

MASCs are also known as Marrow Stem Cell because of their ability to differentiate into tissues derived from the embryonic mesenchyme, specifically bone, cartilage and adipose. We compared the osteogenic and adipogenic potential of SB623 to MASC using standard differentiation protocols.

After several weeks of differentiation, the osteogenic cells were stained for bone formation with alizarin red and the adipogenic cells stained for fat with Oil Red O. The results are shown below in Figure 5.

Figure 5 Differentiation potential of MASC and SB623



Cells were grown in osteogenic and adipogenic media (plus or minus BMP6) for several weeks and then stained with Alizarin Red (bone) or Oil Red O (fat).

MASC cells readily differentiated in to bone and adipose as expected. On the other hand, SB623 cells are dramatically attenuated in their ability to differentiate into these tissues. This has been demonstrated for multiple lots of SB623 (not shown). These finding suggest that SB623 may be less likely than MASC to form ectopic bone or fat after implantation *in vivo*.

3.2.1.6 Anti-inflammatory and Immunosuppressive Properties

Bone marrow stromal cells, also known as mesenchymal stem cells (MSCs) or marrow-adherent stem cells (MASCs) are known to have anti-inflammatory and immunosuppressive properties. Since SB623 cells are derived from MASCs, the anti-inflammatory and immunosuppressive properties of these cells were assessed. In a Mixed Lymphocyte

Reaction (MLR), immune cells from two unrelated donors are mixed and immune cell activation and proliferation are measured as an indicator of adaptive and innate immune activity. The results from this experiment demonstrated that, in the presence of SB623 cells, the activation and proliferation of T cells is attenuated. In another series of experiments the effects of SB623 on dendritic cell formation was measured, since dendritic cells are the primary initiators of the T cell response in the MLR. To assess the impact of SB623 cells on dendritic cells, a co-culture assay between immature dendritic cells and SB623 cells was performed. The results demonstrated that SB623 cells reduce the levels of co-stimulatory molecules on dendritic cells. Collectively, these anti-inflammatory and immunosuppressive properties may contribute to SB623's regenerative properties and seem to obviate the need for immunosuppressive drugs during SB623 therapy.

3.2.2 In Vivo Stroke Models

3.2.2.1 Study N-030

Therapeutic Benefits of SB623 in Experimental Stroke

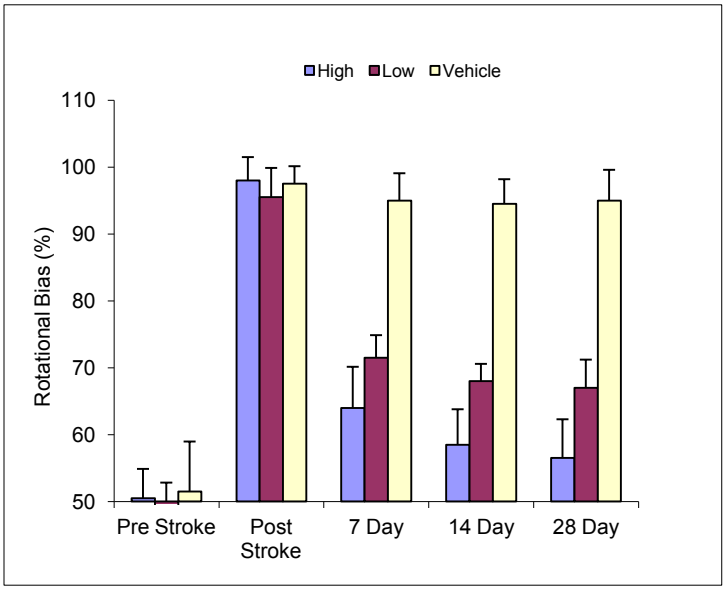
SB623 cells or vehicle were implanted into the striatum of male Sprague-Dawley rats that had been stroked with the MCAo procedure in the right hemisphere, and immunosuppressed with CsA, 10 mg/kg/day i.p. At 4 weeks post-stroke, 3 groups of 10 animals each were implanted with either 90,000 SB623 cells (low dose), 180,000 SB623 cells (high dose) or an equivalent volume of sterile buffer alone (vehicle). Rats were immunosuppressed throughout the planned one-month post-transplantation survival time. Behavioral measurements were made pre-stroke, immediately post-stroke, and at 7 days, 14 days, and 28 days post-stroke.

At 7 days and up to one month post-transplantation, the animals treated with SB623 cells showed significant behavioral improvement ($p \leq 0.00001$) with both the elevated body swing test and the Bederson score compared to the control group, with the higher dose of SB623 cells suggesting a trend of improvement compared to the lower dose.[41] See Figure 6 and Figure 7.

Histological evaluation of the brain at 28 days using the anti-human nuclear antibody HuNu showed 7-9% cell survival. Staining with MAP2, a neuronal marker along with HuNu showed that < 1% of the cells had differentiated along a neural pathway. Nissl staining revealed a significant rescue of the ischemic penumbra, with 45% cell loss in the control animals and 20% in the treated animals, regardless of dose ($p<0.01$).

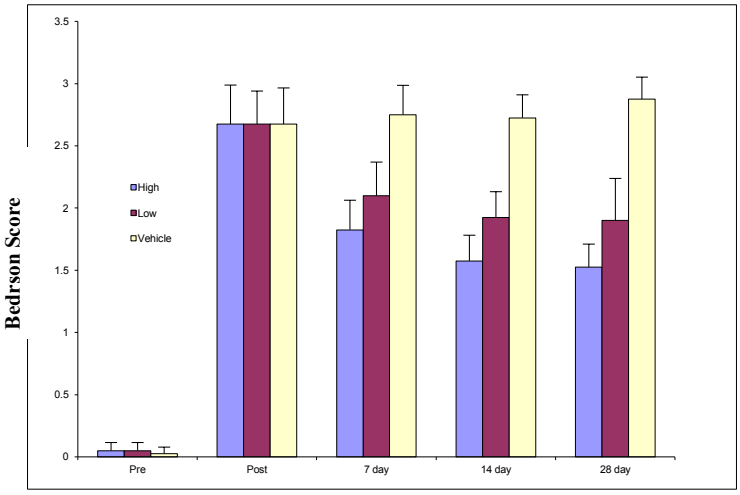
Overall, the positive behavioral outcomes and the relatively low number of engrafted cells in this study point more to a trophic support mechanism rather than to one of cell replacement.

Figure 6 Elevated Body Swing Test: 1-Month Rat Study



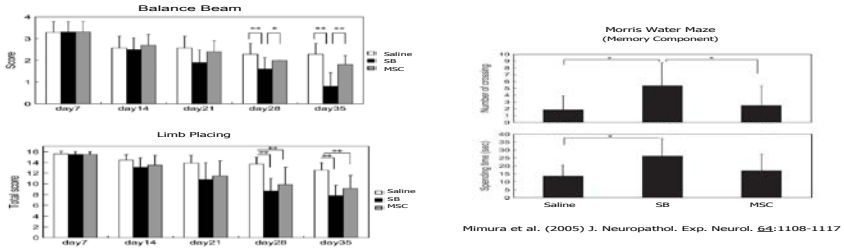
The Elevated Body Swing Test shows SB623 cells promote stroke recovery. Pre-stroke the animals had no rotational bias after lifting by the tail (50%). The animals showed typical defective movement behavior post-stroke (near 100%) bias. Low dose (90,000 SB623 cells) and high dose (180,000 cells) improved over the course of the 28 day study.

Figure 7 Bederson Neurologic Exam: 1-Month Rat Study



SB623 cells at both doses caused an improvement in the multicomponent Bederson neurological score post-stroke.

Figure 8 Comparison of SB623 and MSC in MCAo Rat Model



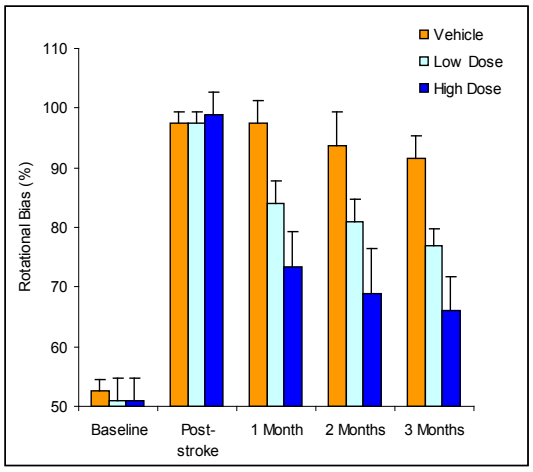
A published study comparing MASC (MSC) and rat-derived SB623-like cells shows superior benefit in balance beam, limb placing and Morris water maze.

3.2.2.2 Study N-034

Therapeutic Benefits of SB-623 in Experimental Stroke[41]

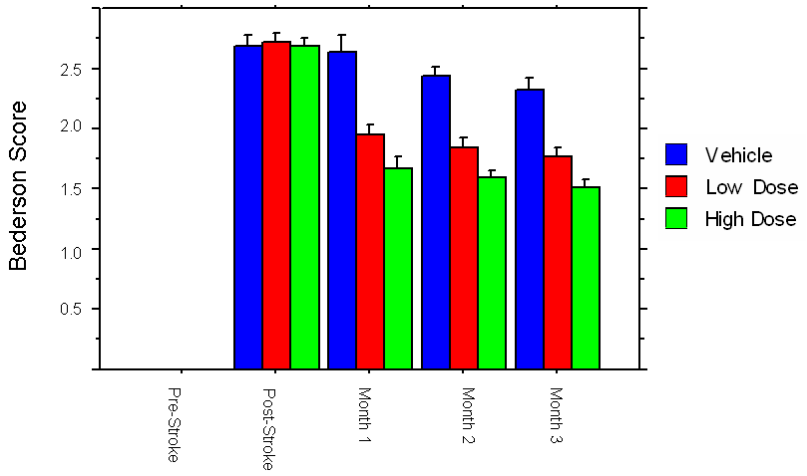
SB623 cells were implanted into the striatum of male Sprague-Dawley rats at 4 weeks post-MCAo stroke with either 90,000 SB623 cells (low dose), 180,000 SB623 cells (high dose) or an equivalent volume of sterile buffer alone (vehicle). Rats were immunosuppressed daily with cyclosporine A (CsA, 10 mg/kg, i.p.) throughout the planned three-month post-transplantation survival time. Behavior evaluations were conducted monthly through month 3. At 1 month and up to three months post-transplantation, the animals treated with SB623 cells showed significant behavioral improvement compared to the control group, with the higher dose of SB623 cells showing a strong trend of improvement compared to the lower dose.[41] See Figure 9 and Figure 10 below.

Figure 9 Elevated Body Swing Test: 3-Month Rat Study



SB623 cells show enduring benefit in EBST scores over 3 months. A trend in dose response is evident.

Figure 10 Bederson Neurologic Exam: 3-Month Rat Study



A similar 3 month benefit is seen in the same animals using the multi-component Bederson neurological score.

The one-hour MCAo stroke surgery produced consistent behavioral impairments at one month post-stroke as revealed by significant biased swing activity and neurological deficits in EBST and Bederson exam, respectively, compared to pre-stroke performance of the animals in both tests. Pair-wise comparisons between pre-stroke and post-stroke performance of the animals revealed significant impairments in both tests (p's < 0.0001) in all stroke animals included in this study.

Following random assignments of the stroke animals to either vehicle, low dose 90,000 SB623, or high dose 180,000 SB623, ANOVA revealed significant effects for both tests (p's < 0.0001). Those that received the high 180k SB623 or low dose 90k SB-623 displayed significant attenuation of behavioral deficits in both tests compared to vehicle-treated stroke animals (p's < 0.0001). This behavioral recovery by SB-623 transplanted stroke animals was sustained at 1, 2, and 3 months post-transplantation and showed a trend of a dose-response.

At each month post-transplantation, each group of animals was euthanized and perfused with saline and formalin for immunohistochemistry and histological examination. Brains were removed and post-fixed in formalin in PBS followed by sucrose in phosphate buffer. Thereafter, cryostat sectioned tissues were obtained. Coronal sections from the ischemic striatal penumbra in each animal were stained with Nissl, a marker of ischemic cell death. Examination revealed that the stroke animals that received vehicle alone exhibited abundant ischemic cell death characterized by cells with swollen or damaged cell membrane. The stroke animals that received low or high dose SB-623 cells displayed obviously fewer numbers of ischemic cells, indicating reduction in ischemic cell death in these transplanted animals. Free-floating sections were incubated with the antibodies MAP2 (a marker of immature neurons) and HuNu (a marker of human cells). Brain sections from each group (*i.e.*, months 1, 2, and 3) showed the presence of human cells. Samples from the higher-dose groups showed more double-labeling that those from the lower-dose groups. A small percentage of the HuNu-positive cells also stained positive with NeuN, a maker of mature neurons. None of the HuNu-positive cells stained positive with the glia marker GFAP.

3.2.2.3 Study N-035

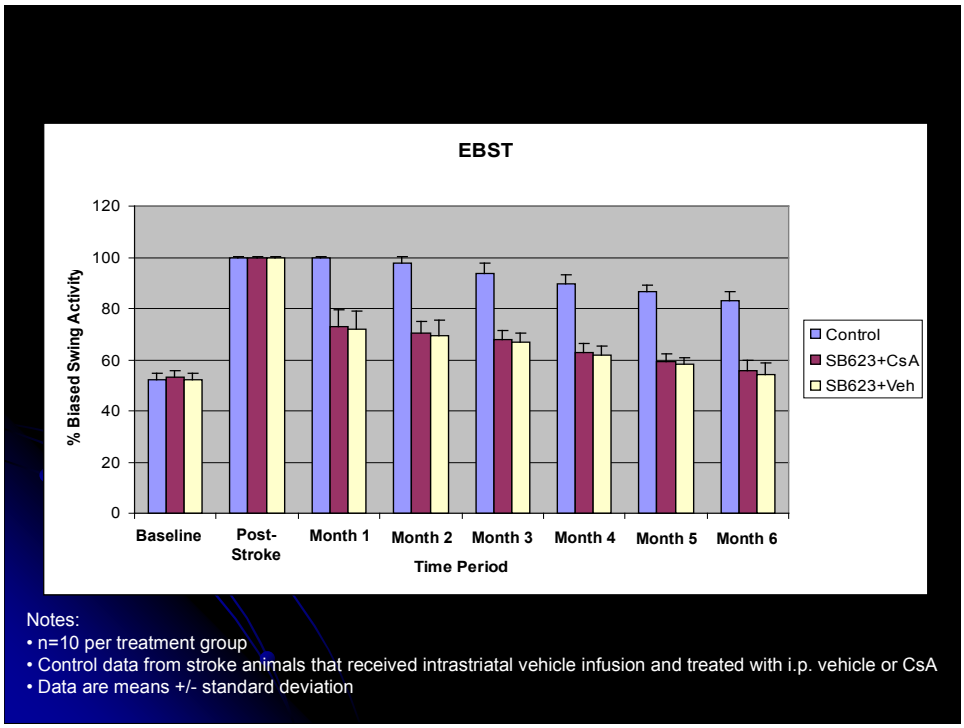
Therapeutic Benefits of SB-623 in Experimental Stroke with/without CsA: 6-mo. Study[42]

SB623 cells were implanted into the striatum of male Sprague-Dawley rats at 4 weeks post-MCAo stroke with 180,000 SB623 cells or an equivalent volume of sterile buffer alone (vehicle), with two control groups. One group of cell-treated rats and one group of control rats were immunosuppressed daily with cyclosporine A (CsA, 10 mg/kg, i.p.) throughout the planned six-month post-transplantation survival time. Similarly, one group of cell-treated rats received no CsA and one group of control rats received no CsA. Behavior evaluations were conducted monthly through month 6. At 1 month and through 6 months post-transplantation, both groups of animals treated with SB623 cells showed significant behavioral improvement on all behavioral measures compared to the control groups, with no differences between groups receiving or not receiving CsA. This is illustrated in Figure 12 below for the Elevated Body Swing Test. Similar significant results were also obtained for the Forelimb Akinesia, Paw Grasp, and Balance Beam tests. See the Investigator's Drug Brochure for further details.

Histological evaluation of the brains of the stroke animals that received SB623 or vehicle, with or without immunosuppression displayed no eventful inflammation or immune response. There was no obvious difference between vehicle treatment groups and transplanted groups, indicating that such increased immunoreactivity was due to the stroke insult and not the transplants. Further, the intensities of immunoreactivity of the astrocyte marker GFAP, the leukocyte marker CD11b, the macrophage/microglia marker Iba1, and the T cell marker CD3 were comparable across all treatment groups. The lack of differences in these inflammatory and immune markers across groups clearly indicates that intracerebral transplantation of human SB623 cells in stroke rats did not elicit overt host reaction. Moreover, these observations also reveal that immunosuppression is not needed to prevent inflammatory response of the host tissue following SB623 transplantation.

SB623 cell grafts did not reduce the extent of core cerebral infarction, the transplants significantly enhance the survival of host cells in the peri-infarct area (Figures 7-12). In view of graft survival being sporadic at 6 months post-transplantation (Figures 13-14), the plausible mode of action of SB623 grafts in promoting behavioral recovery and histological rescue of the peri-infarct area is likely not via cell replacement but due to secretion of growth factors by either the transplants or the SB623-stimulated host tissue.

Figure 11 CsA is not Needed for Long-Term Improvement of Stroke Deficits



The conclusions were:[42]

For behavioral recovery in stroke animals following SB623 transplants:

- Recovery of motor and neurologic functions in stroke rats was sustained up to 6 months post-transplantation, which appeared to improve over time
- Immunosuppression was confirmed to be not critical in promoting and maintenance of behavioral improvement in ischemic stroke rats
- No overt behavioral or gross physical side effects in any of the rats enrolled in this long-term study

For host tissue inflammatory and immune status following SB623 transplants:

- There is no observable eventful inflammation or immune response between control and transplanted stroke animals, with or without CsA.
- Overall, the ipsilateral stroke side appears to display slightly higher immunoreactivity across all markers compared to the contralateral non stroke side.
- There is no obvious difference between control groups and transplanted groups, indicating that such increased immunoreactivity in inflammatory and immune markers in the ipsilateral stroke side is due to the stroke insult and not the vehicle infusion or cell transplant.

For rescue of stroke brain following SB623 transplants:

- There is no observable difference in the volume of infarction with or without transplants, and also with or without CsA.
- However, when the number of surviving cells is counted within the peri-infarct area, transplanted stroke animals displayed significantly higher cell survival than vehicle-infused stroke animals.

- The rescue of ischemic peri-infarct area by transplantation of SB623 cells was not affected by immunosuppression, in that with or without CsA, the transplants increased cell survival in the peri-infarct area.

For SB623 graft survival in stroke brain:

- Using human specific antigen antibody, HuNu, we did not detect robust graft survival at 6 months post-transplantation. Only sporadic HuNu positive cells (1-5) in each transplanted brain were observed
- This observed minimal graft survival was not affected by immunosuppression, in that with or without CsA, we only detected a few HuNu positive cells in those stroke animals that received SB623 transplants.

3.3 Mechanism of action

SB623 cells secrete factors that protect other cells from hypoxic injury, as shown with primary neurons and hippocampal slices (see Sections 3.2.1.1 and 3.2.1.2).[43] These factors may provide trophic support to damaged cells *in vivo*. In addition, SB623 cells secrete matrix that provides support for neural cell growth.[44] Additional investigation into the mechanism is ongoing.

3.4 ADME

All available evidence to date indicates that SB623 cells stay within the brain, with no evidence for any movement outside the brain. See below study summary.

Cells implanted in brains are not detectable beyond 1 month in athymic nude rats (see Sections 3.6.1 and 3.6.2) or in immunosuppressed normal Cynomolgus monkeys at 1 month (see section 3.6.6). Studies with SB623 in rat models of stroke found approximately 7-9% of implanted cells survived at 1 mo., with < 1% differentiated along a neural pathway (see Section 3.2.2). This is consistent with results also from a study in a rat model of Parkinson's disease,[45] in which less than 1% of intrastriatal-implanted SB623 cells survived at 3 weeks post-implant. In another study using the stroke rat, cells were not detectable in the brain at 6 mos., regardless of whether the animals had been treated with CsA or not.

3.4.1 PSP021 (N-032)

A 7 day Study of Lot D-24M2P3 SB623 Cells Implanted into the Brain of an Adult Female Immunosuppressed Cynomolgus Monkey

A short-term study in Cynomolgus monkeys was conducted to determine the location, morphology and immunologic response of implanted SB623 cells.[46] A total of 5 X 10^6 SB623 cells from a male donor were implanted each into the cortical left hemisphere and the subcortical right hemisphere of a normal, CsA-treated female Cynomolgus monkey, with observations up to 1 week post-implantation. The injection paradigm was evaluated for potential toxicities in preparation for proposed safety studies in the non-human primate. A method of localizing implanted human SB623 cells was also confirmed in this study.

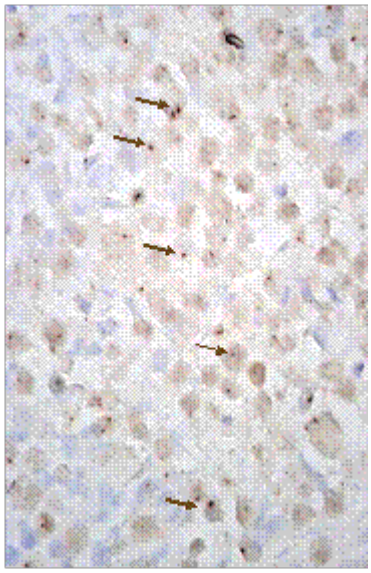
Histological examination of the brain included using Y-chromosome *in situ* hybridization (Y-ISH) staining. Figure 12 shows staining to indicate the needle track for the injection of the cells. Figure 13 shows the areas that appear with Y-ISH staining, indicating the presence of the SB623 cells.

The results of this study found that implanted SB623 cells persist for at least 7 days in the immunosuppressed non-human primate with minimal evidence of cell death or necrosis of the host tissue. The method of delivery used in this study resulted in no local or systemic toxicities at 7 days from either the coordinate placement, volume of infusate injected or the rate of infusion. The Y-chromosome *In Situ* Hybridization method was used to localize human cells implanted to the female non human primate brain in both perfused frozen sections and in perfused, thin paraffin sections.

Figure 12 Primate Needle Track

Male SB623 cells are localize in the female primate brain using Y chromosome in-situ hybridization. SB623 cells show up as brown against a blue background. The needle track is shown.

Figure 13 Primate Y-ISH Staining



A close-up of Y-ISH staining of SB623 cells implanted in primate brain.

3.4.2 MPI 1295-001

I*mplantation of SanBio Cells Into the Brains of Athymic Nude Rats: A Short-Term Biodistribution Study*

The purpose of this study was to test the implantation procedure in athymic rats; determine the post-implantation survival of SB623 cells and the growth of human HT1080 fibrosarcoma cells in the brains of athymic nude rats, and to develop a method of detecting the implanted SB623 cells.

Each rat was mounted in a stereotaxic instrument. Bilateral injections of cell suspensions were made into the cortex and striatum. Four small holes were drilled in the skull at the required coordinates[47] of both the right and left hemispheres (1 cortex and 1 striatal hole per hemisphere). Nine days after surgery, there were two animals in Group 2 (HT1080 fibrosarcoma cells) found dead in their cages. The remaining two animals in this group were observed to have impairment that made it necessary for them to be euthanized *in extremis*. All animals in this group were submitted to necropsy in accordance with the protocol.

Sixteen days after surgery, all four animals in Group 1 (SB623 cells) were submitted to necropsy. No abnormal findings in animals receiving SB623 were observed clinically, macroscopically, or microscopically. No SB623 cells were found in the brain at 16 days post-implant.

3.4.3 N-029

Survival of SB623 Cells Transplanted to the Naïve Adult Rat

This study was designed to assess the feasibility of using SB623 cells in subsequent *in vivo* transplantation models. The endpoints of this study were the acute *in vivo* survival and migratory capacity of SB623 cells transplanted to naïve adult athymic rat brain at 5 hr,, 48 hr, and 14 days post implantation.

A total of 8 rats were used in this study. SB623 cells were stereotaxically implanted into the brains of adult male athymic male rats. Rats were transplanted bilaterally into identical sites in the dorsolateral striatum with approximately 36,000 to 42,000 SB623 cells in 2 uL of modified 1X Dulbecco's phosphate-buffered saline without calcium or magnesium, (DPBS w/o Ca+Mg). Rats were sacrificed at 5h, 48h and 14d post implantation. Cell survival and migratory capacity at the implant site was determined by localizing human derived SB623 cells in perfused sections using human nuclear antigen immunocytochemistry. Sections were counterstained with Nissl or hemotoxylin eosin.

Survival, determined by positive human nuclear (HuNu) antigen staining at 5 hr. and 48 hr. post-implantation, was 16.7% and 9.6%, respectively. Survival at 14 days was 8.2%.

This study confirmed that the SB623 cells transplanted to the striatum of the nude rat have the capacity to survive at acute time points. Furthermore, there was no evidence of extensive migration of implanted SB623 cells.

3.4.4 N-033

A 2-Day Study SB623 Cells Implanted Into The Brains Of Adult Male Athymic Rats; a Comparison of DPBS and Plasma-Lyte A as Formulation Buffers and the Effects of Increased Delivery Rates/Volumes

This study was designed to justify the change from formulation in Dulbecco's Phosphate Buffered Saline (DPBS) to Plasma-Lyte A USP and to determine the impact of doubling the dose, volume and implantation rate to determine if these increases can be used in a planned rat safety study. SB623 cells were implanted bilaterally into the striata of adult male athymic rats and were assessed histologically at 2 days following transplantation.

Cells were suspended in DPBS for implantation into the right hemisphere and in Plasma-Lyte A for implantation into the left hemisphere. The cells were infused into a 2-mm column, depositing 2 uL of cell suspension at 0.5-mm intervals throughout the dorso-ventral length of the column, for a total dose of 230K cells per hemisphere. SB623 cells were visualized by human nuclear antibody immunohistochemistry and showed no significant difference in cell survival at 2d post implantation between cells formulated in DPBS versus Plasma-Lyte A. *In vitro* cell viability and stability at 4 hr. at RT did not differ in either of the two formulation buffers.

Three of the 6 rats injected showed evidence of damage within the striatum. The larger injection volume may have contributed to increased tissue damage and a decreased cell

survival seen in this study compared to previous studies. In addition, the faster rate of cell infusion (2 µL/min *vs.* 1 µL/min) used in the present study may have contributed to apparent compression damage in the host tissue.

We conclude that while doses of 230K cells can be injected into single tracks in the adult rat striatum, these volumes and/or injection rates are not optimal for maximum survival of SB623 cells *in vivo* and appear to be associated with host tissue damage.

The use of DPBS versus Plasma-Lyte A to formulate the cells demonstrated small qualitative differences in the morphology of the cells within the graft core. However; there were no demonstrated significant differences in cell survival *in vivo* or in the *in vitro* stability of the cells following incubation at room temperature for at least 4 hr.

3.5 Overall Preclinical Pharmacology and ADME Summary

Results of all the preclinical pharmacology and ADME studies with SB623 are summarized in Table 1 below.

Table 1 Summary of Preclinical Pharmacology and ADME Studies

Animal Species/Model	Study Type	SB623 Dose, Route	Results	Study Reference
Normal Animal				
Athymic nude rat 8 Animals randomized into 2 groups	16-day pilot study Implant procedure, survival and safety of SB623 cells compared to HT1080 fibrosarcoma cells	0.5 million SB623 cells total dose/animal One time administration Half into each hemisphere, divided into 60% striatum and 40% cortex	No abnormal findings in animals receiving SB623 SB623 cells were found in the brain at 16 days post-implant HT1080-treated animals died or were in extremis by day 9	MPI 1295-001[48] (SanBio PSP010)
Athymic male rat	SB623 *in vivo* survival	36-42,000 SB623 cells total dose/animal One time administration Half into each hemisphere into striatum	No abnormal findings in animals receiving SB623 The percentage survival decreased from 16.7% to 8.2% over 14d. No evidence of extensive migration	N-029 (SanBio PSP006)
Nude rat	Pilot study to develop Y-ish assay	*In vitro* assay development	Y-ish assay is usable for detecting SB623 from male human donors in either rat or monkey tissue	N-031 (SanBio PSP028)
Athymic male rat	Rat survival of cell lot used in the MPI safety study	233,000 cells/hemisphere in either Plasma-Lyte A or DPBS into striatum	Some tissue damage with both vehicles, concluded to be due to larger injection volume and/or more rapid rate of infusion compared to other studies No differences in cell survival between the vehicles *in vivo* or up to 4 hr. *in vitro*	N-033 (SanBio PSP005)

Animal Species/Model	Study Type	SB623 Dose, Route	Results	Study Reference
Cynomolgus Monkey Immunosuppressed with CsA	Pilot primate safety and SB623 survival	One-time administration Total 5.8 million cells per hemisphere in 4 needle tracks in either cortical or subcortical areas)	Minimal evidence of cell death or necrosis of the host tissue No local or systemic toxicities at 7d SB623 cells persist for at least 7d by Y-ish assay	N-032 (SanBio PSP021)
Stroke				
Sprague-Dawley Rat MCAo Stroke Immunosuppressed with CsA	Biodistribution	180,000 cells stereotactically implanted into the striatum	Using qPCR, no SB623 cells were found in spleen, lung, heart, liver, kidney, and testes of stroked animals 2 weeks after implant	Althea 7-RT-SB0102 (SanBio PSP034)
Sprague-Dawley Rat MCAo Stroke Immunosuppressed with CsA	7-day, 14-day, 28-day efficacy and cell survival Vehicle control	One-time administration 90,000 or 180,000 cells, 1 mo. post-MCAo, intrastriatal in right hemisphere	Statistically-significant ($p \leq 0.0001$) improvement with both doses compared to control in both the elevated body swing test and Bederson score at all time points. Cell survival ranged from 5-7% for the two dose levels at 28 days, with < 1% expressing the neuronal marker MAP2. Implantation of SB623 cells resulted in a significant rescue of the ischemic penumbra compared to control ($p<0.01$) regardless of dose.	N-030[41] (SanBio PSP007)

Animal Species/Model	Study Type	SB623 Dose, Route	Results	Study Reference
Sprague-Dawley Rat MCAo Stroke Immunosuppressed with CsA	1-mo., 2-mo., and 3-mo. Efficacy, cell survival and safety Vehicle control	One-time administration 90,000 or 180,000 cells, 1 mo. post-MCAo, intrastriatal in right hemisphere	Statistically-significant ($p \leq 0.0001$) improvement with both doses compared to control in both the elevated body swing test and Bederson score at all time points.	N-034[41] (SanBio PSP027)
Sprague-Dawley Rat MCAo Stroke Comparison with/without CsA	1-6-mo. Efficacy, cell survival and safety Vehicle controls	One-time administration 180,000 cells, 1 mo. post-MCAo, intrastriatal in right hemisphere	Statistically-significant ($p \leq 0.0001$) improvement with both doses compared to control in all motor/neurological measures at all time points. No inflammatory response attributable to the SB623 cells.	N-035[42]

3.6 Toxicology

Three GLP safety studies of SB623 cells have been conducted: a 12-mo. tumorigenicity study in athymic nude rats, a 4-mo. bridging study in athymic nude rats, and a 6-month study in immunosuppressed Cynomolgus monkeys.

3.6.1 12-Month Rat Tumorigenicity

(Study number 1295-002; MPI Research)

The purpose of this GLP study was to assess the possible tumorigenicity of SB623 cells after stereotactic implantation into brains of nude rats. A total of 5 X 10^5 SB623 cells or vehicle were administered into the striatum and cortex of both hemispheres of a total of 120 athymic nude male and female rats further immunosuppressed with the rabbit anti-NK cell antibody Anti-Asialo GM1 (GM1Ab), with observations up to 12 months post-implantation. Two implantations were done in each hemisphere with 10 µL per hemisphere (20 µL per animal): 6 µL into the striatum and 4 µL into the cortex. Animals (15 each per group per sex) were sacrificed at 6 mos. and 12 mos. post-implant.

The endpoints of the study were: clinical observations; clinical pathology at termination; histology of major organs (including brain); cellular markers for presence of SB623, phenotype expression, and inflammation/immune responses.

No SB623 cells, as determined from an anti-human mitochondrial antibody, were found at 6 or 12 months.

There were no adverse cell-related findings in clinical observations or clinical pathology. Histological examination of the brain and other organs and tissues showed no abnormalities that could be attributed to SB623 cells.[49] Because no cells were found at either time point of this study, the biological relevance of these findings may be inconclusive. Minimal to moderate unilateral hydronephrosis was noted in 3 of 13 males from the vehicle group and 6 of 10 males from the 5 x 10^5 SB623 cells group. In addition to the hydronephrosis, infarct and/or chronic inflammation was noted in 3 of 10 males at the dose of 5 x 10^5 SB623 cells. Although there was a higher incidence of renal findings in males treated with SB623, these observations were unilateral in males receiving SB623. Therefore, a test article relationship was considered unlikely.

3.6.2 4-Month Rat Tumorigenicity Bridging Study

(Study number 1295-008; MPI Research)

The purpose of this GLP study was to assess the possible tumorigenicity and survival of SB623 cells after stereotactic implantation into brains of nude rats using identical procedures as with study 1295-008 above, except without a control group. A total of 5 X 10^5 SB623 cells were administered into the striatum and cortex of both hemispheres of a total of 30 athymic nude male and female rats further immunosuppressed with the rabbit anti-NK cell antibody Anti-Asialo GM1 (GM1Ab), with observations up to 4 months post-implantation. Two implantations were done in each hemisphere with 10 µL per hemisphere (20 µL per animal): 6 µL into the striatum and 4 µL into the cortex. Animals (3 per sex per time point) were sacrificed at 2 wks., 1 mo., 2 mos., 3 mos. and 4 mos. post-implant.

The endpoints of the study are clinical observations, clinical pathology, histology of the brain, and cellular markers for presence of SB623 cells at each time point.

SB623 cells, as determined from an anti-human mitochondrial antibody or qPCR, were found at 2 wks., but not at 1 month.[50,51] Determination of the presence of cells by qPCR showed that cells could be detected, but not quantifiable, at 28 days. Cells could not be detected at months 2, 3, or 4.

There have been no adverse cell-related findings in clinical observations or clinical pathology. Histological examination of the brain has shown no abnormalities that could be attributed to SB623 cells. Since cells were found to be present only at the 2-wk. time point, the biological relevance of these findings beyond 2 wks. may be inconclusive.

3.6.3 CsA Dose Selection for Monkey Safety Study

The dose of cyclosporine was based on results of a pharmacokinetic study of i.m. cyclosporine in Cynomolgus monkeys (see Section 3.6.4 below), and a supporting subsequent study also in Cynomolgus monkeys (see Section 3.6.5 also below).

3.6.4 Study Number MPI-004; MPI Research

Three male Cynomolgus monkeys were administered cyclosporine i.m. daily at 15 mg/kg for 4 days. Blood samples for analysis of cyclosporine levels were taken at 0 hr., 1 hr., 2 hr., 3 hr., 5 hr., 8 hr. 12 hr., and 24 hrs. on days 1, 2, and 3 at 24 hrs. Mean trough levels ranged from 463 ng/mL (day 1) to 758 ng/mL (day 3). The conclusion was that a dose of 15 mg/kg i.m. in the Cynomolgus monkey would provide adequate blood levels for the planned safety study with trough levels remaining relatively constant.

3.6.5 One-Month Cynomolgus Monkey +-CsA

(Study number S08-10131, Valley Biosystems and MPI Research)[52]

Two groups of 2 animals each were implanted with SB623 at a dose of 5 X 10^5 cells or vehicle. The striata of the left and right hemispheres of each animal received two injection tracts of 100 µL each consisting of five 20-µL implants. The right hemispheres of each animal received the cells, while the left hemisphere received vehicle only. One group of animals also received Cyclosporine A, 15 mg/kg/day I.M. beginning two days prior to surgery, while the other group received an equivalent amount of vehicle i.m. with the same schedule.

There were no clinical symptoms in the animals that could be attributed to SB623. There were also no adverse hematology or serum chemistry findings that could be attributed to SB623. The brain histological findings were that no SB623 cells were found at 1 month. Further, no histological differences were seen between the brains of any of the animals, or between the hemispheres of each animal.

The conclusions were that immunosuppression in this animal model did not prevent clearance of SB623 by one month and that there were no differences in pathology of the brains comparing with or without CsA.

3.6.6 6-Month Toxicity: Cynomolgus monkey

(Study number 1295-005; MPI Research)

The purpose of this GLP study was to assess the overall safety of SB623 after stereotactic implantation into brains of Cynomolgus monkeys. A total of 5 X 10^6 SB623 cells or vehicle was implanted each into the cortical left hemisphere and the subcortical right hemisphere in

12 normal female Cynomolgus monkeys, immunosuppressed with daily i.m. cyclosporine 15 mg/kg, with observations up to 6 months post-implantation.

Each hemisphere received 2 injection tracks, with each track consisting of two sites, each receiving 50 µL, for a total of 200 µL per hemisphere (5 million cells or vehicle), using a concentration of 25,000 cells/µL or vehicle. Animals (1 control, 3 cells each) were sacrificed at 1 mo., 3 mos., and 6 mos. post-implant.

The endpoints of the study were: clinical observations; clinical pathology at 2 weeks, 1 mo., 3 mos., and 6 mos.; histology of major organs (including brain); and cellular markers for presence of SB623, phenotype expression, and inflammation/immune responses.

No SB623 cells, as determined from an anti-human antibody or a Y-ish assay, were found at 1, 3 or 6 months.

There were no adverse, cell-related findings in clinical observations or clinical pathology. Histological examination of the brain and other organs and tissues showed no abnormalities that were attributed to SB623 cells.[53] Because no cells were found at any time point of this study, the biological relevance of these findings may be inconclusive. One animal in the 91-day recovery group and three animals in the 181-day recovery group that received SB623 cells had an area of necrosis in the external capsule adjacent to the putamen at one or both injection sites. Each area of necrosis measured approximately 1.0 x 0.5 to 3.0 x 0.5 mm in size and was characterized by loss of neuropil with associated reactive gliosis and minimal mononuclear infiltrate including gitter cells. The areas of necrosis observed in these animals were concluded to be most likely due to the act of injection rather than a direct test article effect.

3.7 Summary of Preclinical Safety Studies

See below Table 2 below.

Table 2 Summary of Preclinical Safety Studies

Study Reference	Study Description	Group Size (Species, sex)	Duration/Dose	Route of Admin.	Results/Conclusions
MPI 1295-002 (N-007)	Rat tumorigenicity study: 6 mos. and 12 mos. evaluation; athymic nude rat receiving anti-asialo antibody	60 males: equal control and cells 60 females: equal control and cells	One-time administration Total 0.5 million cells per animal (0.25 million per hemisphere, with 60% in striatum and 40% in cortex in each hemisphere)	Striatum and cortex	No tumors at either 6 mos. or 12 mos. No cell-related adverse findings during the study or at 6 mos. or 12 mos. No SB623 cells were seen at 6 mos.
MPI 1295-008	Rat tumorigenicity bridging study: 1 mo., 2 mos., 3 mos., and 4 mos.	30 animals: 3 per sex per time point	One-time administration Total 0.5 million cells per animal (0.25 million per hemisphere, with 60% in striatum and 40% in cortex in each hemisphere)	Striatum and cortex	No tumors at any time point to date (3 mos.) No cell-related adverse findings. SB623 cells were seen at 2 wks. but not at 1 or 2 mos..
S08-10131	One-month pilot primate safety and SB623 survival comparing with/without CsA at 15 mg/kg/day i.m.	4 females	One time administration with or without CsA Total 5 million cells in the right hemisphere striatum and vehicle in the left hemisphere striatum using 2 injection tracts each with 5 implants.	Striatum	No SB623 cells were found at 1 month. No adverse clinical, laboratory, no histological findings attributable to SB623. No histological differences in the brains or hemispheres

Study Reference	Study Description	Group Size (Species, sex)	Duration/Dose	Route of Admin.	Results/Conclusions
MPI 1295-005 (N-018)	Cynomolgus monkey safety study: 1 mo., 3 mos., and 6 mos. evaluation CsA at 15 mg/kg i.m. daily	9 females with cells 3 females with control vehicle	One-time administration Total 10 million cells per animal (5 million cells per hemisphere in either cortical or subcortical areas)	Subcortical right hemisphere or cortical left hemisphere	No tumors at 1 mo., 3 mos., or 6 mos. No cell-related adverse findings during the study or at 1 mo., 3 mos. or 6 mos. No SB623 cells were seen at 1 mo., 3 mos., or 6 mos.

3.8 Summary of Known and Potential Risks and Benefits

No prior clinical studies with SB623 have been conducted. Based on the available animal data, no risks have been identified, but considerable potential benefit in reversing neurological deficits has been observed in a rat model of stroke.

4.0 DESCRIPTION AND JUSTIFICATION OF TREATMENT REGIMEN

4.1 Dosages

All dosages of cells are to be administered stereotactically through one burr-hole craniostomy using 3 needle tracks within and adjacent to the infarct and 5 cell deposits per track at varying depths, with 20 µL per deposit. Concentrations of cell suspensions to be used will vary depending on the total dosage required per patient. See Table 3 below.

Table 3 Dosages, Volumes and Cell Concentrations

	Total SB623 Cells/Pt.	Total SB623 Cells/Deposit	Total SB623 Cells/Track	Concentration of SB623 Cells per Injection	Total Volume per Deposit, per Track, and Total
Cohort 1	2.5×10^6	1.65×10^5	8.25×10^5	8.3×10^6 cells/mL	20 µL, 100 µL, and 300 µL
Cohort 2:	5.0×10^6	3.3×10^5	16.5×10^5	17×10^6 cells/mL	20 µL, 100 µL, and 300 µL
Cohort 3	10×10^6	6.6×10^5	33×10^5	33×10^6 cells/mL	20 µL, 100 µL, and 300 µL

4.2 Justification

Based on the animal pharmacology and safety studies (see Sections 3.2 and Section 3.6 above), particularly the primate study that used 10 million cells/animal, and considering the larger brain mass of humans, a maximum dose of 10×10^6 SB623 cells and a deposition volume of 20 µL are considered likely to be safe and have a good chance of showing some efficacy. The range of doses, as low as 2.5×10^6 SB623 cells, is considered necessary to observe any possible dose-response trends. The stereotactic surgery procedure to be used (see Section 7.0) has been shown to be safe and well tolerated in another similar study[29,54], and in a retrospective study.[30]

The patient population of 6-60 months post-stroke was chosen to allow for stabilization of motor deficits, particularly after physical therapy, and to allow a sufficient number of patients for reasonable accrual. The duration of time needed for stabilization will vary by patient, with >95% stabilized at 3 mos. post-stroke.[30] Entry criteria to this study require demonstration of stable motor deficit(s) during the prior 3-week period.

5.0 NO CYCLOSPORINE A

5.1 Rationale

The toxicity properties of CsA are well known and present serious risks to patients, particularly older ones. Although most of the toxicity studies summarized in Section 3.6 used CsA, this was done to maximize the chances of uncovering any possible tumorigenicity properties of SB623. Subsequently, it was found that the presence of CsA was not relevant for the pharmacologic activity of SB623 in the MCAo stroke rat model (see Section 3.2.2). Although this is a xeno-transplant model, these findings suggested a need to re-evaluate the need for CsA in all future studies, including clinical. The other animal toxicity studies also indicated that even in immunosuppressed models, SB623 did not survive beyond a month or so, indicating clearance by means of an innate immune response rather than an adaptive one. Finally, an *in vitro* study has shown that SB623 possesses anti-inflammatory and immunosuppressive activity (see Section 3.2.1.6), thus suggesting the possibility that lack of use of CsA may not result in an adverse inflammatory response or any adverse cell-mediated immune response. Nevertheless, careful monitoring will be done to unsure safety of the patients (see below).

5.2 Monitoring for Humoral or Cell-Mediated Immune Response

In the Ph. 1/2a clinical study, Patients will be evaluated on Day 8 after implantation, monthly thereafter through month 4, and then at months 6, 9, 12 and 24 for any symptoms of inflammation, humoral immune response, or cell-mediated immune response (see Table 4). The parameters to be followed are: vital signs, hematology, serum chemistry, lipid panel, cytokine levels (TNF-α, IL-6, IFN-γ), CRP, head MRI, antibodies to SB623, and PBMC function (see Section 15.0).

6.0 STUDY PARAMETERS AND OBJECTIVES

The overall objective of the study is to evaluate the safety and efficacy of SB623 cells stereotactically implanted in the brains of patients with stable stroke.

6.1 Parameters

6.1.1 Safety

- Adverse events
- Serious adverse events (SAE)
- Periodic head MRI scans
- Serum chemistry, hematology, SB623 antibodies to SB623, cytokines, and PBMC function

6.1.2 Efficacy

- Clinical Stroke Evaluations: European Stroke Scale (ESS),[31] NIH Stroke Scale (NIHSS), Modified Rankin Score (MRS), Fugl-Meyer Score,[38] Cognitive Battery (see Appendix D, Section 1.0, Table 7).
- Uptake of fluorodeoxyglucose measured by positron emission tomography (FDG-PET)

6.2 Objectives

6.2.1 Primary Objective

The primary objective is to determine acute and long-term safety of SB623 cells administered stereotactically around the infarct region of brains of patients with stable ischemic stroke.

6.2.2 Secondary Objectives

- To estimate clinical improvement of patients primarily with the ESS and secondarily with the NIHSS, the MRS, the Fugl-Meyer Score and Cognitive Tests
- To estimate metabolic improvement in and around the infarct region using FDG-PET

7.0 SURGICAL AND IMPLANTATION PROCEDURES

The surgical procedure is a modification of one used earlier with another cell product,[29,54] and which has been shown to have a high degree of safety in a retrospective study of over 2,600 patients undergoing stereotactic surgery over the course of 28 years at one major clinic.[30] On the morning of surgery, a standard stereotactic coordinate frame (Leksell Stereotactic System®, manufactured by Elekta[55]) is to be applied to the head under local anesthesia and mild sedation. Either a head CT scan overlaid on the Baseline MRI or a head MRI scan alone is to be performed for stereotactic targeting. The MRI scans are to use insulated posts an RIF transmitter head, and 1.5 tesla. A safe trajectory is to be defined to enter a cortical gyrus, sparing a sulcus. Points are to be determined in the basal ganglia inferior to the stroke and beyond the stroke. Three needle tracks are to be determined with trajectories in the same paramedian plane spaced by 5-6 mm at the target

One burr-hole craniostomy (1-1.5 cm) is to be fashioned under local anesthesia. The dura is to be opened and a 1.8-mm outer-diameter, 15-cm long stabilizing cannula containing a removable solid stylet is to be inserted to a point just proximal to the penumbra of the stroke area. The solid stylet is then to be removed, followed by insertion into the stabilizing cannula of a 0.9-mm outer diameter, 19-cm. long, 20-µL volume Pittsburgh Implantation Cannula (previously qualified for product stability and delivery and provided by the Sponsor) down to the deepest target point for the first implantation. A total volume of 100 µL of cell suspension is to be aspirated into a 100-µL syringe through the implant cannula. The implantation cannula is then to be filled with cell suspension. Five 20-µL volumes of cells are to be injected slowly (approximately 10 µL/min.) into 5 implantation sites, slowly withdrawing the stabilizing needle probe so that the implantations are spaced as equally as possible (intervals of 4-5 mm) with 2-3 implants within the penumbra distal to the stroke area and 2-3 implants within the penumbra proximal to the stroke area. The target locations will be selected by the site neurosurgeon and neurologist to be closest to the motor pathway based on the patient's own neuroanatomy. This procedure is to be repeated with 2 other needle tracks with different trajectories, inserted through the same burr-hole craniostomy.

After completion of the procedure, the patient will receive a CT scan and be admitted to a neurosurgical patient ward for 24 hour observation, during which it is recommended that the patient be on a flat bed with optimal hydration and keeping the subject's head as flat as possible for the next 24 hours. The patient will be discharged on the first post-operative day

unless complications require a longer stay. An MRI is to be done on the first post-operative day (Day 2; see Section 10.5) to insure there are no significant bleeding risks.

8.0 PATIENT SELECTION

8.1 Inclusion Criteria

1. Age 18-75 years
2. Documented history of completed ischemic stroke in subcortical region of MCA or lenticulostriate artery with or without cortical involvement, with correlated findings preferably by MRI or by CT if MRI is contraindicated
3. Between 6 and 60 months post-stroke, and having a motor neurological deficit
4. No significant further improvement with physical therapy/rehabilitation (confirmed by no change in NIHSS greater than ±1 within three weeks prior to enrollment)
5. Modified Rankin Score of 3 or 4
6. NIH Stroke Scale score of >7
7. Two evaluations during prior 3 weeks with no more than ±1 point change in clinical evaluation using the NIH Stroke Scale
8. Able and willing to undergo computed tomography (CT), magnetic resonance imaging (MRI), and positron-emission tomography (PET) scans of the head
9. Agree that use of antiplatelet, anti-coagulant, or non-steroidal anti-inflammatory drugs to be determined by the local medical staff and in accordance with the ACCP 2012 guideline "Perioperative Management of Antithrombotic Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th Edition: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines", if applicable[1], provided that no antiplatelet, anti-coagulant, or non-steroidal anti-inflammatory drugs are to be restarted after surgery until after the Day 8 MRI is read and determined to be safe to re-start
10. Normal emotional status; *i.e.*, no disabling psychological deficits
11. Ability of patient or legal authorized representative to understand and sign an Informed Consent

8.2 Exclusion Criteria

1. History of more than 1 symptomatic stroke
2. History or presence of any other major neurological disease
3. Cerebral infarct size >100 cm^3 measured by MRI
4. Myocardial infarction within prior 6 mos
5. Known presence of any malignancy except squamous or basal cell carcinoma of the skin
6. History of CNS malignancy
7. History of seizures or current use of antiepileptic medication
8. Uncontrolled systemic illness, including, but not limited to: hypertension (systolic >150 mm Hg or diastolic >95); diabetes; renal, hepatic, or cardiac failure
9. Uncontrolled psychiatric illness, including depression (Hamilton Score >14)

10. Total bilirubin >1.5 mg/dL
11. Serum creatinine >1.5 mg/dL
12. Hemoglobin <10.0 g/dL
13. Absolute neutrophil count <2000 /mm^3
14. Lymphocytes <800 /mm^3
15. Platelet count <100,000/mm^3
16. Liver disease supported by AST (SGOT) or ALT (SGPT) ≥2.5 x institutional upper limit of normal
17. Serum calcium >11.5 mg/dl
18. International Normalized Ratio of Prothrombin Time (INR) >1.2
19. Signs and symptoms of intracranial herniation or increased intracranial pressure
20. Acute intracranial hemorrhage
21. Use of neuroleptic drugs
22. Unexplained abnormal preoperative test values (blood tests, electrocardiogram [ECG], chest X-ray); patients with electrocardiographic evidence to suggest a recent myocardial infarction, major dysrhythmia, x-ray evidence of infection, atrial fibrillation, or congestive heart failure will be excluded
23. Participation in any other investigational trial within 4 weeks of initial screening and within 7 weeks of study entry
24. Botulinum toxin injection, phenol injection, intrathecal baclofen, or any other interventional treatments for spasticity (except bracing and splinting) within the previous 3 mos.
25. Ongoing use of herbal or other non-traditional drugs
26. Ongoing drug or alcohol abuse
27. Contraindications to head CT, MRI, or PET
28. Pregnant or lactating
29. Female patients of childbearing potential unwilling to use an adequate birth control method during the first 6 months of the study
30. Presence of serum antibodies to donor SB623 cells with a Luminex value of >1000 MFI (Maximum Fluorescence Intensity): HLA Class I (HLA-A*23:PWMV, HLA-A*68:CGBR; HLA-B*45:FJH, HLA-B*53:KJW; or HLA-Bw4, HLA-Bw6; HLA-Cw*04:SSWB, HLA-Cw*16:01); or Class II (HLA-DRB1 *13:NGUB, HLA-DRB1 *16:02; HLA-DQB1*05:CHZY, HLA-DQB1*05:BK; HLA-DQA1*01:DVB, HLA-DQA1*X, HLA-DRB3,4,5: 3*03:01, HLA-DRB3,4,5: 5*02:02)
31. Any other condition or situation that the investigator believes may interfere with the safety of the subject or the intent and conduct of the study

9.0 INVESTIGATIONAL PLAN

9.1 Overall Study Design

This is an open-label study of stereotactic, intracranial injection of SB623 cells (SB623 cells) in patients with hemiparesis from stable ischemic stroke who have remained stable during the

prior 3 weeks (as documented by NIHSS assessments at weeks -3 and -1). Three cohorts will receive escalating singe doses of SB623, which are to be stereotactically implanted into grey or white matter sites adjacent to the infarct region. One burr-hole craniostomy will be created, and cells implanted using 3 needle tracks with 5 cell deposits for each track at varying depths. Cell implantation will be standardized as to volume (20 µL/deposit) and rate (10 µL/min), with spacing between each implant of approximately 5-6 mm. Each deposit is expected to take approximately 2-3 minutes, with each needle track being completed within 15 minutes. Each cohort will consist of 6 subjects defined by an increasing total number of cells implanted. Safety will be monitored by the Investigator, Principal Monitor, Medical Monitor, and an external Data Safety Monitoring Board (DSMB). For the first cohort, a single patient will first be dosed, then evaluated over a 2 week period for safety prior to dosing the next member of this cohort. This 2-week interval will continue between each of the remaining members of the cohort. If the safety profile is acceptable for a cohort, and after review by the DSMB, the first patient in each subsequent, sequential cohort will be dosed, beginning 4 weeks after dosing of the last patient of the prior cohort. For the second and third patients in each of the subsequent cohorts, there will be an interval of 2 weeks after the prior patients prior to further enrollment.

Safety will be monitored by clinical symptoms, laboratory findings, and MRI brain imaging. Efficacy will be determined based on changes in the clinical measures of stroke and on FDG-PET brain imaging.

A dose-limiting toxicity will be defined as any grade 3 or 4 events which are at least possibly related to study product or administration procedure. If the first patient in a cohort has a dose-limiting toxicity attributable to the SB623 cells, then no further patients will be dosed in that cohort until a comprehensive evaluation has been conducted. If 2 of 6 patients in a cohort have a dose-limiting toxicity attributable to the SB623 cells, then no further patients will be dosed in that or other higher-dose cohorts. Each dose-limiting-toxicity will be evaluated by the DSMB. The DSMB shall be the final arbitrator for attributions.

9.2 Duration of Patient Participation

Two years (except if there is an unresolved Grade 2 adverse event at least possibly related to the therapy, in which case the patient will be followed until resolved or reduced to Grade 1).

10.0 STUDY ASSESSMENTS

10.1 Schedule of Study Activities

Table 4 below lists the procedures to be followed throughout the course of the study.

Table 4 Study Procedures Flow Chart

	Scr. 1	Scr. 2	Baseline[1]	Enroll[2]	Cell Admin	Follow-Up Period							Last Eval.
Study Day			-2 to-1	-1 to 1	1	2	8						
Study Week	-3	-1	1	1	1	1	2						
Study Month								End of 1 and 2	End of 3 and 4	End of 6	End of 9	End of 12	End of 24
Informed Consent	X[3]												
Demographics	X												
Inclusion/Exclusion	X		X										
Medical History	X	X[4]	X[5]	X[6]									
Medication History	X	X[4]	X[5]	X[6]									
Signs & Symptoms	X	X[4]	X[5]	X[6]									
Pregnancy Test[7]	X[8]		X										
Physical Exam.	X		X									X	X
Vital Signs	X	X	X				X	X	X	X	X	X	X
Chest X-Ray and ECG	X												
Hematology (Section 15.3)	X	X	X				X	X	X	X	X	X	X
Serum Chemistry (Sect. 15.3)	X	X	X				X	X	X	X	X	X	X
INR	X		X										
Occult Malig. (Sect. 10.2.2)	X												
Lipid Panel (Section 15.3)			X				X	X	X	X	X	X	X
Cytokines (Section 15.3)			X				X	X (mo. 2)	X (mo. 4)	X	X	X	X
Blood for HLA antibodies	X[9]												
Head CT					X								
Imaging--Head FDG-PET			X							X		X	X
Imaging--Head MRI	X[10]		X		X[11]	X	X	X	X	X	X	X	X

[1] Only after documentation of stable stroke by two evaluations within 3 weeks prior to study entry using the NIH Stroke Scale (no more than ±1 point)
[2] Enrollment only after all inclusion and exclusion criteria are verified and the patient qualifies for the study
[3] Prior to any study-related procedures
[4] Only changes since Screen 1
[5] Only changes since Screen 2
[6] Only changes since Baseline
[7] Only for women of childbearing potential
[8] Serum β-HCG at Screening; serum or urine β-HCG at Baseline
[9] May also be done at a pre-Screen visit
[10] May instead be done at a pre-Screen visit
[11] Or CT overlaid with MRI from Baseline

	Scr. 1	Scr. 2	Baseline[1]	Enroll[2]	Cell Admin	Follow-Up Period							Last Eval.
Study Day			**-2 to-1**	**-1 to 1**	**1**	**2**	**8**						
Study Week	**-3**	**-1**	**1**	**1**	**1**	**1**	**2**						
Study Month								**End of 1 and 2**	**End of 3 and 4**	**End of 6**	**End of 9**	**End of 12**	**End of 24**
Clinical Stroke Evaluations	X[12]	X[12]	X					X	X	X	X	X	X
Cognitive Questionnaire			X							X		X	X
Blood for antibodies to SB623 and for PBMCs			X				X	X (mo. 2)	X (mo. 4)	X	X	X	X
Serum Antibod. (see Sect. 15.6 for assay schedule)													
PBMC Function (see Sect. 15.7 for assay schedule)													
Adverse Events					X	X	X	X	X	X	X	X	X
Concomitant Medications					X	X	X	X	X	X	X	X	X

[12] NIHSS and Modified Rankin at Scr. 1 and only NIHSS at Scr. 2

10.2 Pre-study Evaluation and Baseline (Pre-Screen, Scr. 1, Week -3 and Scr. 2, Week -1)

The following will be done prior to performing any study-specific procedures:

- Informed Consent Signed: study-related details will be carefully discussed with the patient. The patient will sign an Informed Consent Form approved by the local Ethics Committee.

10.2.1 Pre-Screen (Optional)

- Blood sample for determination of presence of antibodies to donor SB623 cells with a Luminex value of >1000 MFI (Maximum Fluorescence Intensity): HLA Class I (HLA-A*23:PWMV, HLA-A*68:CGBR; HLA-B*45:FJH, HLA-B*53:KJW; or HLA-Bw4, HLA-Bw6; HLA-Cw*04:SSWB, HLA-Cw*16:01); or Class II (HLA-DRB1 *13:NGUB, HLA-DRB1 *16:02; HLA-DQB1*05:CHZY, HLA-DQB1*05:BK; HLA-DQA1*01:DVB, HLA-DQA1*X, HLA-DRB3,4,5: 3*03:01, HLA-DRB3,4,5: 5*02:02)
- Head MRI

10.2.2 Scr. 1, Week -3

- Inclusion/Exclusion Criteria
- Demographics
- Medical History
- Medication History
- Signs & Symptoms
- Pregnancy Test (serum β-hCG)
- Physical Exam.
- Vital Signs Including Weight
- Chest X-Ray and ECG
- Hematology (Section 15.3)
- Serum Chemistry (Section 15.3)
- INR
- Determination of occult malignancy by occult blood in stools (hemocult test), finding on chest x-ray, carcinoembryonic antigen, prostate-specific antigen (males only), cancer antigen 125 (females only), α-fetoprotein, and β-hCG
- Blood sample for determination of presence of serum antibodies to donor SB623 cells with a Luminex value of >1000 MFI (Maximum Fluorescence Intensity): HLA Class I (HLA-A*23:PWMV, HLA-A*68:CGBR; HLA-B*45:FJH, HLA-B*53:KJW; or HLA-Bw4, HLA-Bw6; HLA-Cw*04:SSWB, HLA-Cw*16:01); or Class II (HLA-DRB1 *13:NGUB, HLA-DRB1 *16:02; HLA-DQB1*05:CHZY, HLA-DQB1*05:BK; HLA-DQA1*01:DVB, HLA-DQA1*X, HLA-DRB3,4,5: 3*03:01, HLA-DRB3,4,5: 5*02:02)
- Imaging (head MRI: only if not done at a pre-screen visit)

- Clinical Stroke Evaluations (NIHSS and Modified Rankin only)

10.2.3 Scr. 2, Week -1 (±2 Days)

The following will be performed:

- Medical History (only changes since Scr. 1)
- Medication History (only changes since Scr. 1)
- Signs & Symptoms (only changes since Scr. 1)
- Vital Signs
- Hematology (Section 15.3)
- Serum Chemistry (Section 15.3)
- Clinical Stroke Evaluations (NIHSS only)

10.3 Baseline and Enrollment (Days -2 to 1, not including weekends)

10.3.1 Baseline (Weekday -1 to -2)

The following will be performed at Baseline:

- Inclusion/Exclusion
- Medical History (only changes since Screen 2)
- Medication History (only changes since Screen 2)
- Signs & Symptoms (only changes since Screen 2)
- Pregnancy Test (serum or urine β-hCG)
- Physical Exam.
- Vital Signs
- Hematology (Section 15.3)
- Serum Chemistry (Section 15.3)
- INR
- Lipid Panel (Section 15.3)
- Cytokines (Section 15.3)
- Imaging (head MRI & FDG-PET)
- Clinical Stroke Evaluations
- Cognitive Questionnaire (Section 23.0, Table 7)
- Blood for antibodies to SB623 and peripheral blood mononuclear cells (PBMC) function assays and for storage of PBMCs (Section 15.7)
- Luminex assay for antibodies to SB623

10.3.2 Enrollment (Days -1 or 1)

Enrollment can only occur after performing all assessments and verifying that the patient meets the inclusion and exclusion criteria for the study.

10.4 Cell Administration (Day 1)

Prior to any procedures, the patient will be queried on the use of any changes in medication since Baseline.

Prior to cell implantation, either a head CT overlaid with the Baseline head MRI or a head MRI alone will be done to determine the exact locations for the implants.

Using the procedures in Section 6.0, surgical and implantation Procedures and Section 10.4, Preparation and Administration, one burr hole will be made in the skull of the patient in a location that will allow ready access to the infarct region. Cells will be implanted using 3 needle tracks with 5 cell deposits for each track at varying depths. Cell implantation will be standardized as to volume (20 µL/deposit) and rate (10 µL /min), with spacing between each implant of approximately 5-6 mm.

After cell implantation, the following will be performed:

- Imaging (head CT only)
- Adverse Events
- Concomitant medications

10.5 Follow-Up Period (Study Day 2)

The following will be performed:

- Adverse Events
- Concomitant Medications (see Section 12.0)
- Head MRI (MRI must be read before re-starting any antiplatelet, anticoagulant, or non-steroidal anti-inflammatory agents)

10.6 Follow-Up Period (Study Day 8)

The following will be performed:

- Vital Signs
- Hematology (Section 15.3)
- Serum Chemistry (Section 15.3)
- Lipid Panel (Section 15.3)
- Cytokines (Section 15.3)
- Head MRI
- Blood for antibodies to SB623 and peripheral blood mononuclear cells (PBMC) function assays and for storage of PBMCs (Section 15.7)
- Luminex assay for antibodies to SB623 and PBMC function assay
- Adverse Events
- Concomitant Medications (see Section 12.0)

10.7 Follow-Up Period (End of Months 1, 2, 3, 4 ± 5 Days)

- Vital Signs
- Hematology (Section 15.3)
- Serum Chemistry (Section 15.3)
- Lipid Panel (Section 15.3)
- Plasma Cytokines (months 2, 4 only) (Section 15.3)
- Imaging (head MRI)
- Clinical Stroke Evaluations
- Blood for antibodies to SB623 and peripheral blood mononuclear cells (PBMC) function assays and for storage of PBMCs (Months 2, 4 only) (Section 15.7)
- Luminex assay for antibodies to SB623 and PBMC function assay (Months 2, 4 only)
- Adverse Events
- Concomitant Medications (see Section 12.0)

10.8 Follow-Up Period (End of Month 6 ±7 Days)

- Vital Signs
- Hematology (Section 15.3)
- Serum Chemistry (Section 15.3)
- Lipid Panel (Section 15.3)
- Plasma Cytokines (Section 15.3)
- Imaging (head MRI & PET)
- Clinical Stroke Evaluations
- Cognitive Questionnaire (Section 23.0, Table 7)
- Blood for antibodies to SB623 and peripheral blood mononuclear cells (PBMC) function assays and for storage of PBMCs (Section 15.7)
- Luminex assay for antibodies to SB623 and PBMC function assay
- Adverse Events
- Concomitant Medications (see Section 12.0)

10.9 Follow-Up Period (Months 9, 12 ±7 Days)

- Physical Exam. (Month 12 only)
- Vital Signs (Including Weight for Mo. 12 only)
- Hematology (Section 15.3)
- Serum Chemistry (Section 15.3)
- Lipid Panel
- Plasma Cytokines (Section 15.3)
- Imaging--Head MRI
- Imaging—FDG PET (mo. 12 only)

- Clinical Stroke Evaluations
- Cognitive Questionnaire (Month 12 only) (Section 23.0, Table 7)
- Blood for antibodies to SB623 and peripheral blood mononuclear cells (PBMC) function assays and for storage of PBMCs (Month 12 only)
- Luminex assay for antibodies to SB623 and PBMC function assay
- Adverse Events
- Concomitant Medications (see Section 12.0)

10.10 Last Evaluation (End of Month 24 ±14 Days or Early Withdrawal)

- Physical Exam.
- Vital Signs Including Weight
- Hematology (Section 15.3)
- Serum Chemistry (Section 15.3)
- Lipid Panel
- Plasma Cytokines (Section 15.3)
- Imaging (head MRI & PET)
- Clinical Stroke Evaluations
- Cognitive Questionnaire (Section 23.0, Table 7)
- Blood for antibodies to SB623 and peripheral blood mononuclear cells (PBMC) function assays and for storage of PBMCs (Section 15.7)
- Luminex assay for antibodies to SB623 and PBMC function assay
- Adverse Events
- Concomitant Medications (see Section 12.0)

11.0 DESCRIPTION OF STUDY TREATMENT

11.1 Study Drug Description

SB623 cells are provided as a 1-mL sterile cell suspension, containing ≥5 X 10^6 cells/mL, cryopreserved in CryoStore™ freezing media.

11.2 Study Drug Packaging

Individual 1.5-mL Nalgene™ cryovials.

11.3 Study Drug Shipment and Storage

The cryovials containing the frozen cell suspensions are shipped in a dry nitrogen shipper and should be stored in the vapor phase within the shipping container provided by the Sponsor until transferred at the site to a GMP-compliant liquid nitrogen container.

The Sponsor will arrange for Study Drug to be shipped to the clinical site.

11.4 Preparation and Administration

Details for preparation of the cell suspension for administration will be provided by the Sponsor. Clinical sites will be provided necessary materials for reconstitution of the cells and will be trained by the Sponsor. The cryopreserved cells will be thawed, washed, centrifuged, and re-suspended in Plasma-Lyte A at varying concentrations (see Section 4.1) for administration to the patient within approximately 3 hours of re-suspension. Prior to administration, a gram stain and a test for endotoxin will be done and a sterility test initiated on the last cell wash to insure continued sterility. If the endotoxin level is > 5 EU/mL or the gram stain is positive, implantation will not occur. If the sterility test is positive, an investigation will be conducted to determine the source of the contamination. In addition, identification of the pathogen and sensitivity will be done and the patient treated with an appropriate antibiotic. In this event, the patient will be followed closely for adverse events associated with a possible infection and response to antimicrobial therapy, including frequent clinic visits until any infection is cleared.

This Investigational Product may not be used for any purpose other than this clinical study.

11.5 Study Drug Accountability Procedures

The Investigator will be responsible for maintaining inventory and accounting for all Study Drug received from the Sponsor on a drug accountability log. After reconciliation has been completed, all Study Drug vials received by the Investigator (used and unused) will be collected, and the used vials destroyed at the site under supervision of the monitor per institutional standard operating procedure. Unopened vials will be kept frozen until returned to the Sponsor.

12.0 CONCOMITANT MEDICATIONS

All concomitant medications including prescription and over-the-counter drugs taken during the 14 days prior to enrollment or used anytime during the study through 2 years post Study Drug will be documented. Documentation (through month 9 only) will include changes from the prior visit, start and stop dates, dose, and reasons for the medication use.

Investigational drugs or devices for any other indication are not allowed during the study.

13.0 STUDY WITHDRAWAL/TERMINATION

13.1 Study Termination

The protocol may be terminated at anytime by the Sponsor in the event of significant Study-Drug-related adverse effects.

13.2 Site Termination

The study site will be closed if there is evidence of fraud, other unethical conduct, or significant non-compliance to the protocol or to Good Clinical Practices (GCPs). Should patient enrollment be unsatisfactory, or data recording be inaccurate and/or incomplete, the Sponsor may terminate the study and remove all study materials from the study site.

13.3 Patient Discontinuation

Patients will be free to discontinue from the study at any time without giving a reason(s). Patients will be considered discontinued from the study in the event of any of the following reasons:

- Withdrawal of the patient's consent for any reason
- Investigator's discretion due to patient's medical condition

If patient withdrawal occurs during the study period, the Last Evaluation visit should be performed, whenever possible, at the time of patient withdrawal or as soon as possible (see Section 10.8). The Investigator should continue to evaluate the medical condition of any patient who has withdrawn for 2 years post-implant.

In the event a patient withdraws from the study for any reason, the Investigator must notify the Principal Monitor by telephone within 24 hours of withdrawal.

13.4 Patients Lost to Follow Up

Patients who cannot be reached after at least three attempts will be categorized as lost to follow up. The attempts to reach the patients must be documented, with at least one of the attempts written and sent to the patient via certified mail. Patients lost to follow up will still be included in the analysis of the study.

14.0 STOPPING RULES

A dose-limiting toxicity will be defined as any grade 3 or 4 events which are at least possibly related to study product or administration procedure. If the first patient in a cohort has a dose-limiting toxicity attributable to the SB623 cells, then no further patients will be dosed in that cohort until a comprehensive evaluation has been conducted. If 2 of 6 patients in a cohort have a dose-limiting toxicity attributable to the SB623 cells, then no further patients will be dosed in that or higher-dose cohorts. Each dose-limiting-toxicity will be evaluated by the DSMB.

In addition, adverse events attributable to the surgical procedure, such as intracranial infection, intracranial bleeding, or seizures, shall be subject to review by the DSMB

The DSMB shall be the final arbitrator for attributions.

15.0 CLINICAL AND LABORATORY EVALUATIONS AND PROCEDURES

15.1 Medical History

Medical history will include significant medical conditions and surgical history, medications taken within 2 weeks prior to signing the Informed Consent, and signs and symptoms occurring within 3 weeks after signing the Informed Consent.

15.2 Physical Examination and Vital Signs

A complete physical examination will be performed (including a genital/rectal exam if clinically indicated).

Vital signs will include oral temperature, blood pressure at rest, heart rate, and respiratory rate (and Weight for Weeks -3, and Mos. 12, 24).

15.3 Safety Laboratory

All safety laboratory evaluations will be conducted at the laboratories located at or associated with the clinical site. At every sampling time point, approximately 5 mL of blood will be drawn for each of the hematology and serum chemistry panels.

The following laboratory evaluations will be performed:

- Hematology Panel: hematocrit, hemoglobin, WBC, platelet count, lymphocyte count, neutrophil count
- Serum Chemistry Panel: sodium, chloride, calcium, potassium, magnesium, bicarbonate, lactate, C-reactive protein, glucose, creatinine, BUN, AST, ALT, alkaline phosphatase, and total bilirubin
- Lipid Panel: total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides
- Cytokines: Plasma TNF-α, Plasma IL-6, and Plasma IFN-γ
- INR

15.4 Pregnancy Test: Serum or urine β-hCG

- Serum β-hCG at Screening 1 (using same blood draw as for serum chemistry)
- Urine β-hCG at Baseline

15.5 Antibodies to HLA Antigens on SB623

- A serum sample, taken at initial screening (and optionally at a Pre-Screening visit) will be used to determine the presence of antibodies to donor SB623 cells with a Luminex value of >1000 MFI (Maximum Fluorescence Intensity): HLA Class I (HLA-A*23:PWMV, HLA-A*68:CGBR; HLA-B*45:FJH, HLA-B*53:KJW; or HLA-Bw4, HLA-Bw6; HLA-Cw*04:SSWB, HLA-Cw*16:01); or Class II (HLA-DRB1 *13:NGUB, HLA-DRB1 *16:02; HLA-DQB1*05:CHZY, HLA-DQB1*05:BK; HLA-DQA1*01:DVB, HLA-DQA1*X, HLA-DRB3,4,5: 3*03:01, HLA-DRB3,4,5: 5*02:02)

15.6 Serum Antibodies to SB623

Serum antibody measurements will be made to monitor a possible humoral-mediated immune response. Blood samples (approximately 10 mL) will also be taken at the intervals indicated in Table 4 for measurements of serum antibodies to SB623 using the Luminex assay. Assays may be done bimonthly on pooled samples.

15.7 PBMC Function

PBMC function will be evaluated to monitor any possible cell-mediated immune responses, including inflammation.

Blood samples (approximately 20 mL) will also be taken at the intervals indicated in Table 4. PBMCs from Baseline Samples will be aliquoted into approximately 20 tubes to provide at least 600,000 cells per tube, then kept frozen in vapor phase of liquid nitrogen until needed as controls for subsequent time-point assays. For all other time points, PBMCs will be isolated and the sample split into multiple vials of equal portions (A and B) containing at least 600,000 cells each, then similarly frozen until time to assay PBMC function. PBMC function during the study will be determined on the A portions by stimulation with

PMA/ionomycin/SB623, evaluating any changes from baseline in cytokine secretion. These evaluations on batched samples of PBMCs will be approximately at bimonthly intervals during the first 6 months, quarterly thereafter through the first year, then at 2 years.

B portions of PBMCs will be stored in the vapor phase of liquid nitrogen until requested by the Sponsor for any subsequent determination of PBMC function if needed for further safety follow up.

15.8 Clinical Stroke Evaluations

15.8.1 European Stroke Scale (ESS)

Specific information on scoring using the ESS[31] can be found in the publicatin.

15.8.2 National Institute of Health (NIH) Stroke Scale

Specific information on scoring using the NIH Stroke Scale[56] can be found in the publication.

15.8.3 Modified Rankin Scale (MRS)

Specific information on scoring using the MRS[34,35] can be found in the publications.

15.8.4 Fugl-Meyer Score

Specific information on scoring using the Fugl-Meyer Scale[38] can be found in the publication.

15.9 Cognitive Questionnaire

A battery of tests will be used to evaluate cognitive function. These are summarized in Table 7, Appendix D, Section 23.0. Additional details will be provided by the Sponsor.

15.10 Assessment of Cellular Metabolism

Functional assessment of cells within and around the infarct will be determined by use of ^{18}F-fluorodeoxyglucose uptake measured by positron emission tomography (PET).

16.0 ADVERSE EVENTS

16.1 General Information

An **adverse event** (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This includes any side effects, injury, toxicity, or sensitivity reaction, and may include a single symptom or sign, a set of related symptoms or signs, or a disease. An adverse event is also any laboratory abnormality judged to be clinically significant by the Investigator or Sub-investigator(s) that worsened compared to Baseline.

Throughout the course of the study, every effort should be made to remain alert to possible adverse experiences. Patients should be encouraged to report adverse events spontaneously or in response to general, non-directed questioning.

With the occurrence of an adverse event, the primary concern is the safety of the patient. If necessary, appropriate medical intervention should be provided, and the investigational drug discontinued.

An AE **does not** include:

- Medical or surgical procedures (*e.g.*, surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an adverse event
- Pre-existing diseases or conditions present or detected at the start of the study that do not worsen in severity or frequency
- Situations where an untoward medical occurrence has not occurred (*e.g.*, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose of either Study Drug or concomitant medication without any signs or symptoms

A **Serious Adverse Event (SAE)** is any adverse event that results in any of the following:

- death,
- life-threatening event,
- hospitalization or prolongation of hospitalization,
- a persistent or significant disability/incapacity,
- congenital anomaly/birth defect, or
- an event that may require intervention to prevent any one of the other outcomes listed above (based on medical judgment)

An **Unexpected Adverse Event** is any AE that is not identified in nature, severity, or frequency in the current Investigator's Drug Brochure or product information. For this study, an unexpected adverse event also includes neurological deterioration, procedural complications, seizures, benign and malignant tumors and pregnancy, and will be submitted as expedited reports.

An **Unexpected Adverse Drug Reaction** (**ADR**) is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (*e.g.*, Investigator's Brochure for an unapproved investigational medicinal product). All noxious and unintended responses to a medicinal product related to any dose should be considered ADRs. All serious and unexpected ADRs will have expedited reporting to the FDA.

16.2 Adverse Event Reporting Period

The adverse event reporting period for this trial begins upon receiving the first dose of Study Drug and ends 24 weeks after the administration of SB623.

All AEs (both serious and non-serious) must be followed until resolution or until a stable clinical endpoint is reached. All measures required for AE management and the ultimate outcome of the AE must be recorded in the source document and reported to the Sponsor.

16.3 Recording of AEs

All AEs, regardless of severity, seriousness, or presumed relationship to Study Drug, must be recorded using medical terminology in the source document and on the CRF. Events will be recorded at all study sites using standard terminology provided by the Sponsor or designate (*e.g.*, CRO), such as COSTART terminology.

The WHO (World Health Organization) Standard Toxicity Criteria (STC) will be used to assist in categorizing and grading adverse events. A copy of the WHO STC will be provided in the study documents. Whenever possible, a diagnosis should be given when signs and symptoms are due to common etiology (*e.g.*, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection").

16.4 Assessing Relationship of AE to Study Drug

The Investigator must record his/her opinion concerning the relationship of the AE to study therapy on the Adverse Event CRF. Table 5 below provides guidance for assigning relationship to Study Drug.

Table 5 Relationship of Adverse Event to the Administration of the Study Drug

Unrelated	There is not a temporal relationship to study drug administration (e.g., too early, too late, or study drug not taken), or there is a reasonable causal relationship between another drug, concurrent disease, or circumstance and the AE.
Unlikely	There is a temporal relationship to study drug administration, but there is not a reasonable causal relationship between the study drug and the AE (*i.e.*, the AE is doubtfully related to study drug)
Possibly	There is a reasonable causal relationship between the study drug and the AE. Information related to withdrawal of study drug is lacking or unclear
Probably	There is a reasonable causal relationship between the study drug and the AE. The event responds to withdrawal of study drug. Re-challenge is not required
Definitely	There is a reasonable causal relationship between the study drug and the AE. The event responds to withdrawal of study drug, and recurs with re-challenge, when clinically feasible

16.5 Reporting Serious or Unexpected AEs

Any Serious Adverse Event, including death that occurs during this study (from the first dose of Study Drug up to and including 4 weeks following the last dose of Study Drug), whether or not the event is considered to be related to the study treatment, must be reported immediately **(within 24 hours after the site becomes aware of the event)** to the Principal Monitor.

The contact information for reporting SAEs is as follows:

Ernest Yankee, Ph.D.
Phone: 650-625-8965 ext 44
Cell: 650-892-4448
Email: ernest.yankee@san-bio.com

The Investigator is encouraged to discuss with the Principal Monitor any adverse experiences for which the issue of reportability is unclear or questioned.

A verbal or faxed Serious Adverse Event Report must be followed by a written report signed by the Investigator within 48 hours. Written notification must include SAE start and stop dates, Study Drug dosage and treatment history, description of SAE with applicable laboratory test results, list of concomitant medications, relationship of Study Drug to SAE, autopsy report (if applicable), and any other relevant information such as medical history, hospital discharge summary, *etc*. The report should be as complete as possible without delaying Sponsor notification.

An SAE Report should be prepared containing as much available information concerning the event as possible so that a written report can be filed with the appropriate regulatory authorities. Any SAE follow-up information requested by the Sponsor or the Sponsor's designee should be provided in a timely manner.

Upon receipt of notification of any Serious Adverse Event, the Sponsor will immediately conduct an evaluation of the event and take action indicated by the results of the evaluation. This may include notification of the FDA, other Investigators, IRBs and/or the suspension or termination of the study. The Investigator is required to report Serious Adverse Events and Unexpected Adverse Events to the local Ethics Committee (EC) or Institutional Review Board (IRB) in accordance with the EC/IRB bylaws.

All additional follow-up evaluations of the SAE must be reported to the Sponsor. These data should be faxed to the Principal Monitor at 650-625-8472 as soon as they are available.

16.6 Follow-up of Adverse Events

All AEs (both serious and non-serious) should be followed until resolution or until a stable clinical endpoint is reached. All measures required for AE management and the ultimate outcome of the AE must be recorded in the source document and reported to the Sponsor.

17.0 EXTERNAL DATA SAFETY MONITORING BOARD

An External Data Safety Monitoring Board (DSMB) will continuously evaluate toxicity and mortality rates, and recommend appropriate actions, according to the DSMB Charter.

18.0 STATISTICAL METHODS

18.1 Overview of Analysis

18.1.1 Safety Parameters

- Adverse events related to the surgical procedure
- SB623-related adverse events
- Adverse changes imaged by head MRI (edema, adverse anatomical changes)
- Serious adverse events (SAEs)
- Serum chemistry and hematology

18.1.2 Efficacy Parameters

- Clinical improvement of stroke symptoms using the European Stroke Scale, the NIH Stroke Scale, and the Modified Rankin Scale; improvement in motor functions using the Fugl-Meyer scale, and improvement in cognitive status using a test battery (including Rey Complex Figure Test; see Appendix D)
- Increase in fluorodeoxyglucose (FDG) uptake measured by PET

18.1.3 Efficacy Objectives

Primary:

- To evaluate clinical (ESS) and radiographic (FDG-PET) response to 3 dose levels of intracranial administration of SB623 cells at 6 months

Secondary:

- To evaluate clinical (NIHSS, MRS, Fugl-Meyer, Cognitive Tests) response to 3 dose levels of intracranial administration of SB623 cells at 6 months
- To evaluate clinical (ESS, NIHSS), MRS, and Fugl-Meyer response to 3 dose levels of intracranial administration of SB623 cells at 1, 2, 3, 4, 9, 12, and 24 months; also to evaluate changes from Baseline in cognitive function at 6, 12, and 24 mos., and changes from Baseline in radiographic (DFG-PET) responses at 6, 12, and 24 mos.

18.2 Patients to be Included in the Analyses

18.2.1 Efficacy Population

The intent-to-treat (ITT) population will include all enrolled patients, including those who were discontinued from the study or withdrawn for any reason. The Evaluable population will be defined in the Statistical Analysis Plan.

18.2.2 Safety Population

The safety analyses will include all enrolled patients who have received Study Drug and who have any post-Baseline data.

18.3 Analysis of Efficacy

18.3.1 *Primary Analysis*

The primary analysis will be a pooled analysis of changes at 6 months from Baseline for all patients for ESS and FDG-PET parameters. Categorical variables will be summarized by frequency and percent. Continuous variable data will be summarized, including mean, median, standard deviation and range. Statistics will be done on changes in scores, and will be based on Wilcoxon Signed Rank test unless otherwise specified in the Statistical Analysis Plan.

18.3.2 Secondary Analyses

The secondary analyses will be pooled analyses of changes from Baseline at 1, 2, 3, 4, 6, 9, 12, and 24 months for all patients for ESS, NIHSS, MRS, and Fugl-Meyer. Evaluation of changes from Baseline for Cognitive Tests, and FDG-PET parameters will be done at months 6, 12, and 24. In addition, possible dose-response will be determined. Statistics will be done as for the Primary Analysis.

18.4 Analysis of Safety

Adverse events, clinical laboratory data, and vital signs will be analyzed to evaluate the safety of SB623 for all patients in the Safety population through 2 years after the dose of Study Drug.

A treatment-emergent adverse event will be defined as any event not present prior to the initiation of treatment or any event already present that worsens in either intensity or frequency following exposure to study treatment.

All adverse event data will be listed per patient including severity, relationship to Study Drug, and action taken. Frequency within each treatment group of each type of adverse event will be summarized using an acceptable coding dictionary.

Laboratory data and vital signs will be listed by patient. Laboratory data values above and below normal ranges which are considered clinically significant will be indicated on the listing. Descriptive statistics will be displayed for each laboratory parameter and vital sign assessment at each time point. The mean change from baseline in each of these continuous variables will also be described.

18.5 Determination of Sample Size

The sample size of 6 patients per cohort was determined based on safety considerations. Based on the animal safety studies, no dose-limiting toxicity is anticipated. However, if the true rate is 40%, a sample size of 6 patients per cohort would result in a < 5% chance of missing a dose-limiting toxicity.

18.6 Deviations from the Protocol Analysis Plan

Any deviations from the original planned analysis as described in the protocol will be detailed in the final integrated clinical report with an explanation of the alternative methods employed.

19.0 ADMINISTRATION OF THE STUDY

19.1 Regulatory Considerations

This study will be conducted in compliance with the protocol, ICH Good Clinical Practice Guidelines (GCPs), and the applicable local regulatory requirements. This study will be conducted in accordance with the ethical principles that originate in the Declaration of Helsinki and ICH Guidelines for Good Clinical Practices (GCPs).

Study protocols and Informed Consent Forms will be approved by the appropriate Ethics Committee or Institutional Review Board (and governmental authorities, as needed) prior to initiation of the study at a particular site. All patients will sign an Informed Consent Form prior to any study-specific procedures. Performance during the study will be routinely monitored by a study monitor selected by the Sponsor.

19.2 Independent Ethics Committee (EC)/Institutional Review Board (IRB)

The Investigator must submit the final protocol and proposed informed consent document to an Independent Ethics Committee (EC) or Institutional Review Board (IRB) that complies with the ICH Guideline for Good Clinical Practice. The EC/IRB will provide the Investigator with a written decision regarding the conduct of the study at that site and a copy

of the document will be forwarded to the Project Manager. The study will not be initiated and patients will not be enrolled until the appropriate documentation of EC/IRB approval of the study protocol and the informed consent has been received.

Substantive modifications to the protocol will be submitted to the EC/IRB for approval. These modifications may be implemented only after EC/IRB written approval has been received and forwarded to the Project Manager. Administrative changes to the protocol such as a change that has no effect on the conduct of the study or risk to the patient should be submitted to the EC/IRB for review, but formal approval is not required.

The Investigator must also submit any other written information that will be given to the study patients as well as any advertisements for patient recruitment, if used, to the EC/IRB for approval prior to implementing these documents.

The Investigator will make appropriate and timely reports to the EC/IRB as required by applicable government regulations and EC/IRB policy. In addition to progress reports, all known information regarding serious adverse events, whether observed at their clinical site or at another site participating in a clinical investigation with the Study Drug, will be reported to the EC/IRB. It is the Sponsor and/or its designee's responsibility to inform the Investigator of serious adverse events observed at other investigational sites.

It is the Investigator's obligation to provide the Sponsor and/or its designees with copies of all study-related correspondence with the EC/IRB in a timely fashion and to retain originals in a file. This EC/IRB correspondence file will be made available as requested to appropriate designees for monitoring or quality assurance review and to governmental regulatory representatives during site audits.

19.3 Patient Information and Informed Consent

Written informed consent must be obtained from each patient after the nature of the study has been fully explained in accordance with the ICH Guideline for Good Clinical Practice. Informed consent must be obtained prior to performing any study-specific procedures. The consent form that is used must be approved by both the reviewing EC/IRB and by the Sponsor.

The patient (or surrogate) and the individual explaining the study will sign the current EC/IRB-approved version of the consent form. A copy of the signed consent form will be given to the patient. The date that consent was obtained will be recorded on the case report form as well as in the patient's chart.

A copy of the EC/IRB-approved version of the consent form will be provided to the Sponsor. Original signed consent form must be maintained at the site and be made available for inspection, as appropriate.

A sample consent form is provided in Appendix A.

19.4 Adherence to the Protocol

The study shall be conducted as described in this protocol except for an emergency situation in which proper care of the patient requires immediate alternative intervention. This protocol refers to the protocol as provided by the Sponsor and approved by both the IRB and the FDA. All of these versions of the protocol must be the same. While FDA regulations permit the protocol to be amended, this must be done in accordance with the provisions agreed upon on

Section 19.5. Any deviation from the design of the study as set forth in this document must be recorded as a protocol deviation and be explained in detail as it occurs and/or is detected.

19.5 Protocol Modifications

Neither the Investigators nor the Sponsor will modify this protocol without obtaining the concurrence of the other. All protocol amendments will be issued by the Sponsor, and must be signed and dated by the Investigator prior to implementation of the amendment. The Sponsor will submit protocol modifications to Regulatory Agencies as required. The Investigator is responsible for notifying the EC/IRB of changes. Substantive changes will require EC/IRB approval, such as changes in experimental procedures that affect patient safety, changes in dosage or study treatment, changes in assessment parameters, or changes in patient eligibility criteria. The EC/IRB may require the Informed Consent Form to be altered in the event of protocol changes or new safety information.

In situations requiring a departure from the protocol, the Investigator or other physician in attendance will contact the Sponsor or designee by fax or telephone. If possible, this contact will occur before implementing any departure from protocol. In all cases, contact with the Sponsor or designee must be made as soon as possible in order to discuss the situation and agree on an appropriate course of action. The CRF and source document must describe any departure from the protocol and the circumstances.

19.6 Data Collection

Patient screening/enrollment will be documented in a study-specific log at the study site. This log will capture the following information: patient number, initials, patient personal identification number or medical record number, date of screen/enrollment, reason for not enrolling (if applicable), and any comments.

A CRF (Case Report Form) will be provided for each study patient. Data collected through the completion of experimental procedures required by this protocol will be recorded in the patient's chart as source documentation. This data will then be transcribed onto the CRF.

All required study data, including results of an autopsy if the patient dies during the study, will be entered into the Case Report Forms (CRFs) provided by the Sponsor. All information in the CRFs must be supported by original data in the patient's medical records. All medical records, laboratory printouts, notes made by the physician, and other materials such as x-rays will be considered source data and must be available for inspection by the Sponsor and/or delegates, or governmental representatives.

All entries to the CRF must be made in indelible black ink. All corrections must be made by drawing a single line through the error and entering the correct data as close as possible to the original entry without obscuring data. The correction must be initialed and dated by the person making the correction. The Investigator remains responsible for the accuracy and adequacy of all data entered on CRFs.

Data will be monitored as described in Section 19.8. Under direction of the clinical monitor, CRFs will be pulled and further processed for data entry and analysis. A copy of each CRF page must remain at the investigative site in the appropriate patient's CRF binder.

Upon further data processing, queries may be generated and sent to the Investigator for clarification or correction. The Investigator will address any queries and forward resolutions as directed by the site monitor.

19.7 Maintaining Records

A study binder must be maintained at the investigative site and must contain the documents identified in Appendix B, including a signed Investigator Agreement. The Sponsor, or its designee, will provide a Study Binder to the site.

According to U.S. Federal Regulations (21 CFR 312), all records related to this clinical trial must be retained by the Investigator for at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications OR until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The Sponsor will inform the Investigator as to when these documents no longer need to be retained. These documents must be stored in a safe location and be available in the event of a regulatory audit.

Study records that must be retained include, but are not necessarily limited to: patient charts, case report forms, product disposition records, essential documents identified in Appendix B, and study reports.

19.8 Monitoring, Auditing, Inspecting

The Sponsor or designee (*e.g.*, clinical research organization [CRO]) will assure the accuracy of data, the selection of qualified Investigators, appropriate study centers and review protocol procedures with the Investigators and associated personnel prior to the study and during periodic monitoring visits. The Sponsor or a designee will review CRFs for accuracy and completeness during on-site monitoring visits and after their return from the clinical site. Discrepancies will be resolved with the Investigator as appropriate.

The Sponsor or its designees will monitor the study using the following methods:

- frequent telephone contacts
- periodic site visits
- review of original patient records, case report forms, drug accountability and storage, and general study documentation

So that the study may be adequately monitored, the Investigator will cooperate in providing the Sponsor's designees with all study documents *(e.g.*, patient charts and study files) and responding to inquiries that may arise as a result of the document review.

Review of these documents will usually occur during a routine monitoring visit, but may also be required during a visit by a quality assurance auditor. The Investigator will also provide access to these records to regulatory representatives if and when requested. The Sponsor reserves the right to terminate the study site if access to source documentation of work performed in this study is denied to the Sponsor or regulatory representatives.

19.9 Confidentiality

The anonymity of patients participating in this study must be maintained. Patients will be identified by their assigned patient number and their initials in all written communications between the Investigator and Sponsor. Documents that are not submitted to the Sponsor and

that identify the patient (*e.g.*, signed informed consent; source documents/charts) will be made available to the Sponsor or regulatory authorities for inspections, but will be maintained in confidence.

All study related information provided by the Sponsor to the Investigator and not previously published, including but not limited to the active study agent identity, the investigator's brochure, the study protocol, verbal and written communication, case report forms, assay methods and scientific data, will be considered confidential. In addition, all information developed during the conduct of the clinical investigation of the study agent is also considered confidential. Neither the Investigator nor any of his/her employees or agents shall disclose or use this information for any purpose other than the performance of the clinical study. Such information shall remain the confidential and proprietary property of the Sponsor, and disclosure to others will be limited to other physicians who are conducting studies with the same active study agent, the Ethics Committee/IRB and the applicable regulatory authorities except by prior written permission of the Sponsor or its agents. At such time that information becomes widely and publicly available through no fault of the Investigator, the obligation of nondisclosure toward that particular information will cease.

19.10 Publication Policy

Publication of the results of this study may be appropriate. At least 30 days prior to expected submission to the intended publisher or meeting committee, the Investigator must submit a copy of the desired presentation (oral or written) or publication manuscript to the Sponsor. This review period may be shortened upon mutual consent where circumstances require expeditious review. The Sponsor reserves the right to suggest modification of any publication, presentation or use by the Investigator if such activity may jeopardize a patent application, an existing patent, or other proprietary rights.

20.0 APPENDIX A: SAMPLE INFORMED CONSENT

(Final version to follow institutional standards)

Patient Initials ____ ____ ____

Date ___ / ___ / ___

AUTHORIZATION TO PARTICIPATE IN A RESEARCH PROJECT

TITLE OF STUDY:

A Phase 1/2A Study of the Safety and Efficacy of Modified Stromal Cells (SB623) in Patients with Stable Ischemic Stroke

SPONSOR: SanBio, Inc.
231 S. Whisman Rd.
Mountain View, CA 94041

PROTOCOL NO.: SB-STR01

INVESTIGATOR:

TELEPHONE:

STUDY SITE LOCATION:

INTRODUCTION:

You are being invited to take part in a research study that will last approximately 24 months for you. Approximately 18 patients will participate in this study. It is important that you read and understand several general principles that apply to all study participants:

1. Taking part in the study is entirely voluntary
2. You do not have to be in any research study offered to you by your doctor. When you are deciding if you should join the study, you may want to talk with someone not part of the study about your questions and feelings about joining. This could be a family member, friend, or another health provider
3. Personal benefit to you (improvement in your stroke symptoms) may or may not result from taking part in the study. Knowledge will be gained from your participation that may benefit other patients.
4. You may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled.

The nature of the study, the benefits, risks, discomforts and other information about the study are discussed below. There may be information in this consent form that you do not understand. Any questions you have should be discussed with the staff members. They will explain it to you.

NOTE: If you are not completely truthful with your study doctor regarding your health history, you may harm yourself by participating in this study.

THE NATURE AND PURPOSE OF THIS STUDY:

You have been diagnosed with stable ischemic stroke, and have had physical therapy for your stroke-related conditions. Your stroke was caused by a blood clot in a blood vessel in your brain and this happened at least 6 months ago, but not more than 60 months ago. This study is being conducted primarily to determine the safety of a cell suspension of SB623 cells administered by injection into your brain around the area of the stroke. In addition, information will be obtained to determine if there might be any improvement in the severity of your stroke. All the usual standard of care procedures and drugs will also be used.

SB623 cells are modified cells derived from bone marrow of other adult humans. From the bone marrow, cells are isolated and then modified using recombinant DNA methods to make cells that have been shown to secrete agents that may be helpful to dying tissue. The product that you will be using is an investigational drug (not approved by any governmental regulatory authorities).

EXPLANATION OF PROCEDURES TO BE FOLLOWED:

After you sign the consent form and before you begin treatment, you will be asked questions about your medical history, medications you are taking, and how you feel. You will also have a complete physical examination. The doctor will check your pulse, blood pressure, respiratory rate and temperature.

Approximately 25 mL (a little less than one ounce or two tablespoons) of blood will be drawn and a urine sample will be requested for monitoring your health status and to confirm that you are eligible to participate in the study. If you are a woman capable of bearing a child, the blood sample will also be used for a pregnancy test.

You will be evaluated for your stroke symptoms by a variety of methods, such as asking you questions and requesting you to make certain movements while you are being videotaped. This will be done twice prior to implantation of the SB623 cells, over a three week period. This is to confirm that your stroke symptoms are stable.

You will also be asked to undergo magnetic resonance imaging (MRI) of your head at your first screening visit. The purpose of the MRI is to determine the precise location and size of your stroke and to ensure there are no other abnormalities. MRI machines only use a magnetic field. In addition, the PET scan will require that you be injected with an agent that contains a radioactive tag so that the wellness of the cells in and around your stroke area can be evaluated.

Surgical Procedure and Administration of the Cells:

The SB623 cells are to be implanted directly into your brain in and around the area of the stroke. To do this, you will have a small hole drilled into your skull. This will be done under local anesthesia. The exact position of the hole to be made will be determined by having you undergo MRI scanning. MRI (Magnetic Resonance Imaging) is a special procedure using an instrument with a very strong magnet. A special apparatus will be used on your head to make sure the hole is positioned such that the implantation of the cells will be precisely into the stroke region, at location also determined by MRI. A needle will be inserted through the hole into your brain extending into and slightly beyond the main stroke region. Cells will be implanted at 5 sites through this one needle injection. Two additional needle insertions with 5 more implantation sites each will also be done at slightly different angles.

There will be 3 groups of patients enrolled in this study. Your assignment to a particular group by the study doctor will depend on when you enter the study. Six patients will be studied in group 1 before proceeding to 6 patients in group 2, who in turn will be studied before proceeding to 6 patients in group 3. The total amount of cells you will receive will depend on which group you are in. Group 1 patients will receive 2.5 million cells; group 2 patients will receive 5 million cells; and group 3 patients will receive 10 million cells. All patients will receive a total of 300 µL of fluid (about $1/3^{rd}$ of mL, or less than $1/10^{th}$ of a teaspoon or about 6 drops from a standard dropper).

Study Procedures:

You will be asked to provide blood samples throughout the study in addition to any samples required for your normal care. Approximately 25 mL (a little less than one ounce or two tablespoons) of blood will be drawn at total of 11 times, including the screening and baseline samples. These will be used to monitor safety and to assess certain markers related to the cells.

After completion of the surgical and cell injection procedures, you will be given CT scan (a type of imaging procedure using a contrast agent and X-rays) to determine that you have no complications, and then will be admitted to a neurosurgical patient ward for 24 hour observation. You will be discharged on the first post-operative day.

Periodically, you will also receive a PET scan. PET stands for Positron Emission Tomography. In this procedure, a marker similar to glucose (a sugar) containing an atom that emits radiation (positron) will be injected into your blood stream. A machine that measures this radiation will determine if your brain cells are behaving in the usual manner in absorbing the glucose marker.

You will be asked to periodically undergo additional MRI scans to assess your progress and to evaluate safety. You will also be asked standardized questions about your stroke symptoms and be asked to make certain movements as you did during your screening.

REQUEST FOR AUTOPSY:

In the event of your death during the study from any cause, the study doctor will ask your family for permission to perform an autopsy. The evaluation of organs and tissues after death is a very valuable method to learn more about any effects of the study agent. You should talk about the possibility of an autopsy with your family and health provider, and advise them of your wishes. The study sponsor will pay all costs of the autopsy.

POSSIBLE RISKS AND DISCOMFORTS:

This is the first time that SB623 cells have been administered to people, so possible side effects are not known, except that mild, post-surgical headache that resolved within 1 week has been reported by all 6 of the first cohort of subjects.. It has been administered to animals (rats and monkeys) with no negative cell-related effects observed. Since the cells did not survive longer than 3 months in rats, possible later cell effects could not be determined.

Studies with SB623 cells to determine its capability to cause harm to an unborn child have not been performed. Therefore, if you are pregnant, or think you might be, you will not be allowed to participate in this study. If you are a woman of childbearing potential, you will be tested for pregnancy at the beginning of the study.

Because you will be receiving a CT scan, you will be exposed to a low level of radiation. The risks of the contrast material used with the CT scan include rare allergic reactions, nausea, flushing, low blood pressure, asthma, stroke and organ damage. The PET scans will also expose you to a low level of radiation from the injected radioactive agent (FDG).

Although animal studies up to 12 months have shown no evidence of any tumor formation, there is the theoretical possibility that SB623 may induce formation of tumors, as has been seen with embryonic stem cells. While this is believed to be very unlikely to occur with SB623, periodic MRI measurements will be carried out to provide an early indication if this should happen.

All of the animal safety studies have used animal models that were highly immunosuppressed to uncover any possible tumor formation. However, you will not be given any immunosuppressant during this study since other studies have suggested that SB623 is itself an immunosuppressant. Nevertheless, there is a possibility that implantation of SB623 could cause local inflammation or a systemic immune response. This will be monitored carefully during the study by making measurements of your blood that include standard laboratory tests and by periodic MRI scans as indicated earlier.

The surgical procedure that you will receive has been associated with a small risk of bleeding and infection. This was documented by studying the records of over 2,650 patients who had undergone this surgical procedure over a period of 28 years. Headaches are a normal and expected symptom following surgery for cell implantation, as is mild pain at the site of the incision. These symptoms may last for several days following your operation. So far, this study has demonstrated a small risk of a special bleeding problem, so-called subacute subdural hematoma, which is a bleed deep in the brain where the needle was inserted. Should this occur, it will be managed by the current standard of care, which may necessitate another surgical procedure to remove the blood. There may also be a small amount of cerebral spinal fluid associated with this, which may also require surgical removal. One subject has also had seizure that was readily treated. This was categorized as possibly related to the surgery, and unrelated to the Study Drug.

Significant new information that becomes known during the course of the research that may affect your willingness to continue participation in the study will be provided to you.

If you experience more than minimal discomfort after completing the implantation procedure, you should:

1. **Call the study doctor at once at telephone number: (xxx) xxx-xxxx**
2. **If necessary, go to the nearest emergency room**

During this study, you will receive the standard care for your condition (including antibiotics, pain medicine, cardiovascular support, ventilator support, and hospitalization) as required.

PREGNANCY/ BIRTH CONTROL:

If you are pregnant or nursing a child, you cannot take part in this study since there is no known information about potential harm to unborn children. If you are a woman who has had a tubal ligation, hysterectomy, or are post-menopausal, you may be eligible to take part in this study. If you are a woman of child-bearing potential you must practice acceptable methods of birth control (oral, implantable, or injectable contraceptives; spermicide in conjunction with a barrier such as a condom or diaphragm; intrauterine device or IUD) for at least the first 6 months of the study.

ALTERNATIVES TO PARTICIPATION:

There are no approved therapies for your stroke-related condition. The study doctor has discussed any other options available to you, including non-participation in this study. If you decide not to take part in this study, it will not affect your future treatment.

POSSIBLE BENEFITS:

Although it is hoped that participation in this trial may lead to some improvement in your condition, the primary goal of this study is to establish safety of the approach rather than to maximize the chance for improvement. Accordingly, you should not expect to receive benefit from participation in this study. However, the knowledge obtained from this research may help the health care professionals caring for you to better treat other patients undergoing treatment for a condition similar to yours.

COMPENSATION FOR PARTICIPATION:

There is **no additional cost** to you for participation in this research study beyond the costs normally associated with your treatment. The SB623 cells will be provided free of charge to you by the Sponsor. The physician visits and associated tests related to the study will also be provided at no cost. You will be reimbursed any out-of-pocket expenses relating to participation in this research study.

MEDICAL CARE FOR INJURY RELATED TO THIS STUDY:

In the event of injury resulting from your participation in this research, medical care will be provided to you by the study doctor. The care will be free of charge to you. The Sponsor of the Study is insured in the event you are injured through participation in the study.

CONFIDENTIALITY AND RELEASE OF MEDICAL RECORDS:

The study doctor will provide information about your treatment to the Sponsor (SanBio Incorporated) and/or its representative. You have the right to privacy, and all information obtained in this study that can identify you individually will remain confidential to the extent possible within the state and federal laws. Only your patient number and initials will be

recorded on study documents and reports. Your name will **not** be revealed in any reports or publications resulting from this study. Other information, including your gender, age, and ethnicity, will be recorded on study documents for the purposes of analyses of the study outcome. Nothing in the study documents will provide any identification of you. Governmental and institutional regulatory authorities and the Sponsor and/or its designee (the site monitor), may inspect and copy your records pertaining to this study. The results of the study will be reported to governmental agencies.

In the rare instances for which regulatory authorities may require patient names, the regulatory authorities will treat such information as confidential, but disclosure to third parties may be required on rare occasions. Therefore, absolute protection of confidentiality by regulatory authorities cannot be promised or implied.

Because this study involves genetically-modified cells, safety information must be reported to the Recombinant DNA Advisory Committee of the National Institutes of Health. This information is available to the public. However, no information by which participants can be identified will be reported with the safety information. We will try to keep your identity and other information collected in this study confidential. There may be some exceptions when the law requires disclosure. Representatives of [study site], and/or the Food and Drug Administration, and/or the National Institutes of Health, or other regulatory agencies outside [study site] may ask to review the data collected from this study. These groups can have access to your name and medical records.

It is possible that the media may want to find out about you because you took part in this study. We will take every precaution to protect your privacy and that of your family. We will also maintain the confidentiality of the research data. To lower the chance that your identity will be made public, all requests for information will be directed to the [study site] Public Relations Office. Despite these efforts, reporters may try to find out who you are without the approval of the [study site]. If the media succeed, they might ask to interview you and your privacy may be invaded. Every effort will be made to protect your privacy but it may not be possible to do so.

VOLUNTARY PARTICIPATION AND WITHDRAWAL:

Your participation in this study is voluntary and you are free to withdraw at anytime. Any new information developed during this research that may be related to your willingness to continue participation will be provided to you. Participation or withdrawal will involve no penalties or loss of benefits to which you are otherwise entitled, and will not affect your future medical care.

Your participation in this study may be discontinued without your consent for the following reasons:

- if treatment appears to be medically harmful to you
- if you fail to follow directions for participation in the study
- if it is discovered you do not meet the eligibility requirements
- if the study is canceled

If you withdraw from, or must be discontinued from the study prior to its completion, you will be asked to have a final close out visit to protect your health status.

POSSIBLE CONFLICTS OF INTEREST:

The study doctor is a researcher in this study. As a researcher, he is interested not only in our health and well being, but also in the results of this study. It is possible that sometimes these two goals may conflict with one another. Researchers protect the rights and interests of participants by carefully following the rules of the study.

This research is sponsored by SanBio, Inc. This means that SanBio is paying the research team for the costs of doing the study. The researchers do not have a financial stake in the results of the study.

OFFER TO ANSWER QUESTIONS ABOUT THIS STUDY:

If you have questions about this study, your condition and/or treatment, or if you experience a research-related injury or illness, you should contact **Insert Name of PI, MD at: (xxx) xxx-xxxx**

If you have questions about your rights as a research patient, you may contact a representative of the **Ethics Committee for this institution at (xxx) xxx-xxxx.**

CONSENT TO PARTICIPATE IN THIS STUDY:

Your consent to participate in research should be voluntary and informed. By signing this form, you acknowledge that you have read this information (or had it read to you), been given an opportunity to ask questions about the information provided in this form, and understand the potential risks and benefits. By signing this form you indicate that you wish to participate in the study at this time.

Having consented, you still have the right to withdraw at any time without jeopardy to your care. If you wish to withdraw, you should notify the study doctor or study coordinator; you do not have to give a reason if you do not wish to. You will not lose any legal rights as a research patient by signing this form.

You will be given a signed copy of this form to keep and refer to as needed.

Signature of Study Patient	Date
Printed Name of Study Patient	
Signature of Person Explaining Informed Consent	Date
Title of Person Explaining Informed Consent	

21.0 APPENDIX B: ESSENTIAL STUDY DOCUMENTS

DOCUMENT	LOCATION		COLLECTION TIME		
The following documents will be obtained for the regulatory files at the indicated times during the trial	Sponsor	Site	Pre-Study	During	Post-Study
Investigator's Drug Brochure	X	X	X		
Signed protocol and amendments, if any	X	X	X		
Sample Case-Report Form (CRF)	X	X	X		
Informed-Consent Form	X	X	X		
Any other written information given to trial patients	X	X	X		
Advertisement for patient recruitment, if used		X	X		
Financial aspects of the trial	X	X	X		
Insurance statement, where required	X	X	X		
Signed agreement between: • Investigator/institution and Sponsor • Investigator/institution and CRO, where required • Sponsor and CRO • Investigator/institution and authority(ies), where required	X	X	X		
Dated, documented approval/favorable opinion of IRB/IEC for: • Protocol and any amendments • CRF, if applicable • Informed-Consent Form • Any other written information to be provided to the patient(s) • Advertisements for patient recruitment, if used • Subject compensation, if any • Any other documents given approval/favorable opinion	X	X	X		
IRB/IEC committee composition	X*	X	X		
Regulatory authority(ies) authorization/approval/ notification of protocol, where required	X*	X*	X		
Curriculum vitae and/or other relevant documents evidencing qualifications of Investigator(s) and Sub-investigators	X	X	X		

DOCUMENT	LOCATION		COLLECTION TIME		
The following documents will be obtained for the regulatory files at the indicated times during the trial	**Sponsor**	**Site**	**Pre-Study**	**During**	**Post-Study**
Normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) included in the protocol	X	X	X	X	
Medical/laboratory, technical procedures/tests • Certification or • Accreditation or • Established quality control and/or external quality assessment or • Other validation, where required	X	X*	X		
Sample of label(s) attached to investigational product container(s)	X	X	X		
Instructions for handling of investigational product(s) and trial-related materials, if not included in the protocol or Investigator's Brochure	X	X	X		
Shipping records for investigational product(s) and trial-related materials	X	X	X		
Decoding procedures for blinded trials	X†	X	X		
Investigator's Brochure updates	X	X		X	
Revisions to: • Protocol/amendment(s) • CRF(s) • Informed Consent Form(s) • Any other written information provided to patients • Advertisements for patient recruitment, if used	X	X		X	
Dated, documented approval/favorable opinion of IRB/IEC for: • Protocol amendments • Revisions to Informed-Consent Form • Revisions to any other written information to be provided to the patient • Advertisements for patient recruitment, if used • Any other documents given approval/favorable opinion • Continuing review of trial	X	X		X	

DOCUMENT	LOCATION		COLLECTION TIME		
The following documents will be obtained for the regulatory files at the indicated times during the trial	**Sponsor**	**Site**	**Pre-Study**	**During**	**Post-Study**
Regulatory authority(ies) authorizations/approval/ notifications for protocol amendment(s) and other documents	X	X*		X	
Curriculum vitae for new Investigator(s) and/or Sub-investigators	X	X		X	
Updates to normal value(s)/range(s) for medical laboratory/technical procedure(s)/test(s) included in the protocol	X	X		X	
Updates of medical/laboratory/technical procedures/test • Certification or • Accreditation or • Established quality control and/or external quality assessment or • Other validation, where required	X	X*		X	
Documentation of investigational product(s) and trial-related materials shipment	X	X		X	
Relevant communications other than site visits • Letters • Meeting notes • Notes of telephone calls	X	X		X	
Signed Original Informed-Consent Form		X			
Signed Informed-Consent Form--Copy	X			X	
Source documents		X		X	
Signed, dated, and completed CRFs	X‡	X§		X	
Documentation of CRF corrections	X‡	X§		X	
Notification by originating Investigator to Sponsor of serious adverse events and related reports	X	X		X	
Notification by Sponsor and/or Investigator, where applicable, to regulatory authority(ies) and IRB(s)/IEC(s) of unexpected serious adverse drug reactions and of other safety information	X	X*		X	
Notification by Sponsor to Investigators of safety information	X	X		X	
Interim or annual reports to IRB/IEC and authority(ies)	X*	X		X	
Subject screening log	X*	X		X	
Subject identification code list		X		X	

DOCUMENT	LOCATION		COLLECTION TIME		
The following documents will be obtained for the regulatory files at the indicated times during the trial	**Sponsor**	**Site**	**Pre-Study**	**During**	**Post-Study**
Subject enrollment log-original		X			
Subject enrollment log-copy	X			X	
Investigational product(s) accountability at the site	X	X		X	X
Record of retained body fluids/tissue samples, if any	X	X		X	X
Documentation of investigational product(s) destruction	X	X‖		X	X
Completed patient identification code list		X			X
Final report by Investigator/institution to IRB/IEC where required, and where applicable, to the regulatory authority(ies)	X	X			X
Clinical study report	X	X¶			X

* Where required
† Third party if applicable
‡ Original § Copy
‖ If destroyed at site
¶ If applicable

22.0 APPENDIX C: WHO STANDARD TOXICITY CRITERIA

The WHO Standard Toxicity Criteria is tabulated below in Table 6.

Copies of this document will also be provided to each site as part of the study documents.

For abnormalities not found elsewhere in the WHO table, use the following scale to assign grade or severity:

Grade 1	Mild	Transient of mild discomfort; no limitation in activity; no medical intervention/therapy required.
Grade 2	Moderate	Mild-to-moderate limitation in activity; some assistance may be need. No or minimal medial intervention/therapy required.
Grade 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required; hospitalization or prolongation of current hospitalization possible.
Grade 4	Life-threatening	Extreme limitation in activity, significant assistance required; significant medial intervention/therapy required; hospitalization or prolongation of current hospitalization or hospice care probable.

Table 6 WHO (World Health Organization) Toxicity Criteria by Grade

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Haematology	WBC (x103/l)	4	3.0 - 3.9	2.0 - 2.9	1.0 - 1.9	< 1.0
Haematology	Platelets (x103/l)	WNL	75.0 - normal	50.0 - 74.9	25.0 - 49.9	< 25.0
Haematology	Haemoglobin (g/dl)	WNL	10.0 - normal	8.0 - 9.9	6.5 - 7.9	< 6.5
Haematology	Granulocytes/ Bands (x103/l)	2	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
Haematology	Lymphocytes (x103/l)	2	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
Haematology	Haemorrhage	none	mild, no	gross, 1 - 2 units transfusion per episode	gross, 3 - 4 units transfusion per episode	massive, > 4 units transfusion per episode
Coagulation	Fibrinogen	WNL	0.99 - 0.75 x N	0.74 - 0.50 x N	0.49 - 0.25 x N	< 0.25 x N
Coagulation	Prothrombin time(Quick)	WNL	1.01 - 1.25 x N	1.26 - 1.50 x N	1.51 - 2.00 x N	> 2.00 x N
Coagulation	Partial thromboplastin time	WNL	1.01 - 1.66 x N	1.67 - 2.33 x N	2.34 - 3.00 x N	> 3.00 x N
Metabolic	Hyperglycaemia (mg/dl)	< 116	116 - 160	161 - 250	251 - 500	> 500 or ketoacidosis
Metabolic	Hypoglycaemia (mg/dl)	> 64	55 - 64	40 - 54	30 - 39	< 30
Metabolic	Amylase	WNL	< 1.5 x N	1.5 - 2.0 x N	2.1 - 5.0 N	> 5.0 x N
Metabolic	Hypercalcaemia (mg/dl)	< 10.6	10.6 - 11.5	11.6 - 12.5	12.6 - 13.4	13.5
Metabolic	Hypocalcaemia (mg/dl)	> 8.4	8.4 - 7.8	7.7 - 7.0	6.9 - 6.1	6

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Metabolic	Hypomagnesaemia (mg/dl)	> 1.4	1.4 - 1.2	1.1 - 0.9	0.8 - 0.6	0.5
Gastrointestinal	Nausea	none	able to eat reasonable intake	intake significantly decreased but can eat	no significant intake	—
Gastrointestinal	Vomiting	none	1 episode in 24 hrs	2 - 5 episodes in 24 hrs	6 - 10 episodes in 24 hrs	> 10 episodes in 24 hrs or requiring parenteral support
Gastrointestinal	Diarrhoea	none	increase of 2 - 3 stools / day over pre-Rx	increase of 4 - 6 stools / day, or nocturnal stools, or moderate cramping	increase of 7 - 9 stools / day, or incontinence, or severe cramping	increase of > 10 stools / day or grossly bloody diarrhoea, or need for parenteral support
Gastrointestinal	Stomatitis	none	painless ulcers, erythema, or mild soreness	painful erythema, oedema, or ulcers but can eat solids	painful erythema, oedema, or ulcers and cannot eat solids	requires parenteral or enteral support for alimentation
Liver	Bilirubin (N = 17 µmol/L)	WNL	-----	< 1.5 x N	1.5 - 3.0 x N	> 3.0 x N
Liver	Transaminase (SGOT, SGPT)	WNL	2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N
Liver	Alk Phos or 5 nucleotidase	WNL	< 2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N
Liver	Liver- clinical	No change from baseline	-----	-----	precoma	hepatic coma
Kidney, bladder	Creatinine	WNL	< 1.5 x N	1.5 - 3.0 x N	3.1 - 6.0 x N	> 6.0 x N
Kidney, bladder	Proteinuria	No change	1 (+) or < 0.3 g% or 3 g/L	2 - 3 (+) or 0.3 - 1.0 g% or 3 - 10 g/L	4 (+) or > 1.0 g% or > 10g/L	nephrotic syndrome
Kidney, bladder	Haematuria	Negative	microscopic only	gross, no clots no Rx needed	gross and clots bladder irrigation	requires transfusion or cystectomy

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Kidney, bladder	Weight gain/ loss	< 5.0 %	5.0 - 9.9 %	10.0 - 19.9 %	20.00%	-----
Pulmonary	Pulmonary	none or no change	asymptomatic, with abnormality in PFTs	dyspnoea on significant exertion	dyspnoea at normal level of activity	dyspnoea at rest
Cardiac	Cardiac arrhythmias	none	asymptomatic, transient, requiring no therapy	recurrent or persistent, no therapy required	requires treatment	requires monitoring; or hypotension, or ventricular tachycardia or fibrillation
Cardiac	Cardiac function	none	asymptomatic, decline of resting ejection fraction by less than 20 % of baseline value	asymptomatic, decline of resting ejection fraction by more than 20 % of baseline value	mild CHF, responsive to therapy	severe of refractory CHF
Cardiac	Cardiac ischaemia	none	non-specific T-wave flattening	asymptomatic, ST and T wave changes suggesting ischaemia	angina without evidence of infraction	acute myocardial infarction
Cardiac	Cardiac-pericardial	none	asymptomatic effusion, no intervention required	pericarditis (rub, chest pain, ECG changes)	symptomatic effusion; drainage required	tamponade; drainage urgently required
Cardiac	Hypertension	none or no change	asymptomatic, transient increase by greater than 20 mm Hg (D) or to > 150 / 100 if previously WNL. No treatment required.	recurrent or persistent increase by greater than 20 mm HG (D) or to > 150 / 100 if previously WNL. No treatment required.	requires therapy	hypertensive crisis

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Cardiac	Hypotension	none or no change	changes requiring no therapy (including transient orthostatic hypo-tension)	requires fluid replacement or other therapy but not hospitalisation	requires therapy and hospitalisation; resolves within 48 hours of stopping the agent	requires therapy and hospitalisation for > 48 hrs after stopping the agent
Neurologic	Neuro: sensory	none or no change	mild paraesthesias; loss of deep tendon reflexes	mild or moderate objective sensory loss moderate paraesthesias	severe objective sensory loss or paraesthesias that interfere with function	-----
Neurologic	Neuro: motor	none or no change	subjective weakness; no objective findings	mild objective weakness without significant impairment of function	objective weakness with impairment of function	paralysis
Neurologic	Neuro: cortical	none	mild somnolence or agitation	moderate somnolence or agitation	severe somnolence, (>50 % waking hours), agitation, confusion, disorientation or hallucinations	coma, seizures, toxic psychosis
Neurologic	Neuro: cerebellar	none	slight incoordination, dysdiadochokinesia	intention tremor, dysmetria, slurred speech, nystagmus	locomotor ataxia	cerebellar necrosis
Neurologic	Neuro: mood	no change	mild anxiety or depression	moderate anxiety or depression	severe anxiety or depression	suicidal ideation

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Neurologic	Neuro: headache	none	mild	moderate or severe but transient	unrelenting and severe	-----
Neurologic	Neuro: constipation	none or no change	mild	moderate	severe	ileus > 96 hrs
Neurologic	Neuro: hearing	none or no change	asymptomatic, hearing loss on audiometry only	tinnitus	hearing loss interfering with function but correctable with hearing aid	deafness not correctable
Neurologic	Neuro: vision	none or no change	-----	-----	symptomatic subtotal loss of vision	blindness
Pain	Pain	none	mild	moderate	severe	reg. narcotics
Skin	Skin	none or no change	scattered macular or papular eruption or erythema that is asymptomatic	scattered macular or papular eruption or erythema with pruritus or other associated symptoms	generalised symptomatic macular, papular or vesicular eruption	exfoliative dermatitis or ulcerating dermatitis
Alopecia	Alopecia	no loss	mild hair loss	pronounced or total hair loss	-----	-----
Allergy	Allergy	none	transient rash, drug fever < 38^{o} C (100.4^{o} F)	urticaria, drug fever 38^{o} C (100.4^{o} F), mild bronchospasm	serum sickness, bronchospasm requiring parenteral medication	anaphylaxis
Local	Local	none	pain	pain and swelling with inflammation or phlebitis	ulceration	plastic surgery indicated

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Fever of unknown origin	Fever of unknown origin	none	37.1 - 38.0o C 98.7o - 100.4o F	38.1 - 40.0^{o} C 100.5 - 104^{o} F	> 40.0^{o} C > 104.0^{o} F for less than 24 hrs	> 40.0^{o} C (>104^{o} F) for more than 24 hrs or accompanied by hypotension
Infection	Infection	none	mild	moderate	severe	life-threatening
Additional events	Asthenia	Analogous to Karnofsky index (WHO grading)				
Additional events	Chills	Analogous to fever				
Additional events	Peripheral oedema	analogous to weight gain				
Additional events	Anorexia	analogous to weight loss				

23.0 APPENDIX D: COGNITIVE FUNCTION TEST BATTERY

Table 7 Cognitive Function Test Battery

Estimated Intelligence
*Wechsler Abbreviated Scale of Intelligence (WASI) 2 Test
Language
Controlled Oral Word Association Category
Vocabulary (WASI)
Attention
Trails A Time
Digit Vigilance Accuracy
Learning and Memory
Rey Auditory Learning Test
Rey Complex Figure – immediate & delayed recall
Logical Memory – WMS-III
Working Memory
Trails B Time and Errors
Letter-Number Sequencing- WMS-III
Visuospatial/Constructional Ability
Rey Complex Figure Copy
Matrix Reasoning—WASI
Psychomotor Efficiency
Digit Vigilance Time
Trails A Errors
Digit Symbol Substitution Test -WAIS-III
Grooved Pegboard
Executive Function (reasoning, mental manipulation)
Stroop Interference
Controlled Oral Word Association—FAS
Mood State and Quality of Life
Beck Depression Inventory, 2nd Ed.
Beck Anxiety Inventory

* Baseline only

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