SANBIO INCORPORATED
CLINICAL PROTOCOL

TITLE: A Double-Blind, Controlled Phase 2b Study of the Safety and Efficacy of Modified Stem Cells (SB623) in Patients with Chronic Motor Deficit from Ischemic Stroke

PROTOCOL #:	SB-STR02
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Damien Bates Digitally signed by Damien Bates Date: 2017.01.08 16:14:02 -08'00'	
Signature Date	Signature Date

Investigator Statement

I agree to abide by all the provisions set forth in the attached protocol. I also understand that these materials contain confidential information belonging to SanBio, Inc. Except as may be otherwise agreed to in writing, I agree to hold such information in confidence and not to disclose it to others (except where required by applicable law) nor use it for unauthorized purposes. In the event of actual or suspected breach of this obligation, SanBio, Inc. should be promptly notified.

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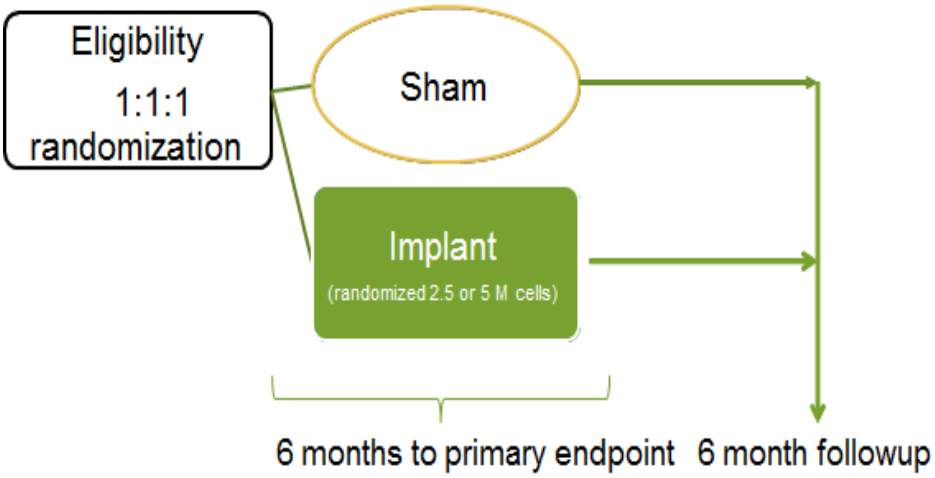
1.0 PROTOCOL SYNOPSIS

Protocol #:	SB-STR02
Title:	A Double-Blind, Controlled Phase 2B Study of the Safety and Efficacy of Modified Stem Cells (SB623) in Patients with Chronic Motor Deficit from Ischemic Stroke
Study Objectives:	Primary: To evaluate the clinical efficacy of intracranial administration of SB623 cells Secondary: To evaluate the effect of intracranial administration of SB623 cells on disability parameters To evaluate the safety and tolerability of intracranial administration of SB623 cells
Background and Rationale	SB623 cells are adult bone-marrow-derived stem 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. A 2 year Phase 1/2a dose escalation study (NCT01287936) of SB623 stereotactically implanted into the brains of patients with chronic motor deficits due to ischemic stroke has been completed. Results of a six-month interim study report of this study have shown statistically-significant improvements in motor function in each of three scales: the European Stroke Scale (ESS), the National Institute of Health Stroke Scale (NIHSS) and the Fugl-Meyer scale. The study showed no serious adverse events attributed to SB623, and only minor adverse events mostly grade 1 or 2 (with one grade 3) that were unrelated, unlikely related, or possibly related to SB623. No dose-limiting toxicities were observed. Based on the Phase 1/2a study, SB-STR01, no safety concerns with SB623 were seen, but efficacy was suggested. Therefore, a double-blind, controlled Phase 2b study is justified using patients who are not as disabled (modified Rankin Score [mRS 2-4]). The primary efficacy endpoint will be the Fugl-Meyer Motor Score (FMMS), with the following scales as secondary endpoints: • Modified Rankin Scale • Action Research Arm Test • Gait Velocity • NeuroQOL (Upper Extremity Function and Lower Extremity Function) • Global Rating of Perceived Change:

	○ By Subject (may be completed by Caregiver) ○ By Clinician.
Study Design	This is a double-blind, sham-surgery controlled study of stereotactic, intracranial injection of SB623 cells in patients with fixed motor deficits from ischemic stroke. The study will be conducted at approximately 65 sites in the United States. Two cohorts, Group 1 (2.5 and 5 million SB623 cells combined) and Group 2 (sham placebo), will be included in this study. Subjects who are randomized into this study will receive either approximately 2.5 million SB623 cells, approximately 5 million SB623 cells, or sham surgery at a 1:1:1 randomization ratio. Randomization will be performed via an interactive web/voice response system (IXRS), stratified by Screening mRS score (recorded in the IXRS at the clinical site).  Note: Group 1 (Implant) will receive either approximately 2.5 million SB623 cells or approximately 5 million SB623 cells. Abbreviation: M = million. The surgical procedure is a modification of one used earlier with another cell product (Kondziolka D, Steinberg GK, Wechsler L, et al. Neurotransplantation for Patients with Subcortical Motor Stroke: A Phase 2 Randomized Trial. J Neurosurg. 2005; 103:38-45), 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 (Lunsford LD, Niranjan A, Khan AA, Kondziolka D. Establishing a Benschmark for Complications Using Frame-Based Stereotactic Surgery. Sterotact Funct Neurosurg. 2008; 86:278-287). This procedure was also used in the ongoing clinical trial SB-STR01. On the morning of surgery, 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 at least 1.5 tesla. Implant sites are to be determined in the subcortical peri-infarct tissue to surround the infarct. Three needle tracks are to be determined with trajectories to surround the infarct, so that cell deposit targets are spaced 5-6 mm apart. Either frameless or frame stereotaxy procedures may be used. <u>Group 1</u> One burr-hole craniostomy (1-1.5 cm) is to be fashioned under local anesthesia and sedation. The aim of the sedation is two-fold: to minimize subject discomfort and to prevent any subject recall or awareness of the procedure to preserve subject

	blinding. The dura is to be opened and a stabilizing cannula (size dependent on the use of a frame or frameless procedure) 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 an implantation cannula (previously qualified for product stability and delivery and provided by the Sponsor, as needed) down to the deepest target point for the first implantation. A safe trajectory to enter a 100 µL of cell suspension is defined. A volume of 125 µL of cells is backloaded into a 100 µL syringe, 25 µL of these cells are injected to clear the implant cannula, thus the final volume in the syringe for implant is 100 µL. Detailed information will be provided separately from this protocol in an Investigational Product Manual. 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 to produce equally spaced implants (intervals of 5-6 mm) within the peri-infarct region extending from inferior to the infarct to superior to the infarct. The target locations will be selected by the site neurosurgeon 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. <u>Group 2</u> Group 2 will receive sham surgery (sedation, stereotactic planning procedure, partial-thickness skull outer table burr hole, scalp suture, but no penetration of inner table or dura mater). This will be done under sedation and local anesthetic. Again the purpose of the sedation is two-fold: to minimize subject discomfort and to prevent any subject recall or awareness of the procedure to preserve subject blinding. The sham surgery procedure will be scripted to mimic as closely as possible the procedure undertaken by Group 1. Subjects in Group 2 will remain in the operating room for the same duration as Group 1. <u>Post-Surgical</u> After completion of the procedure, both groups will receive a CT scan and be admitted to a neurosurgical patient ward for 24 hour observation. 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 prior to discharge (Day 2) to insure there are no significant bleeding risks. The neurological assessment team evaluating Fugl-Meyer and other efficacy endpoints will be blinded, with the subjects also blinded. The surgical team will remain unblinded, any communication between the surgical and neurological team (including the investigator) will be blinded regarding treatment assignment. Safety will be monitored throughout the study. In addition an external Data Safety Monitoring Board will be utilized to review safety data, including clinical symptoms, laboratory findings, and MRI brain imaging. Two or more serious adverse events potentially attributed to SB623 as assessed by the Investigator will trigger a review by the DSMB before continuing enrollment. In addition, the DSMB will review the study for safety at 25%, 50%, and 75% enrollment. The DSMB shall be the final arbitrator for attributions. Efficacy will be determined based on changes in the clinical measures of stroke through standardized assessments (Fugl-Meyer Motor Scale (FMMS), Modified Rankin Scale (mRS), Action Research Arm Test (ARAT), Gait Velocity and two sub-domains of the NeuroQOL scale). MRI of the brain will be performed at scheduled time points (pre- and post-contrast T1 weighted, dual echo, and Fluid Attenuated Inversion Recovery [FLAIR] sequences). MRIs will be analyzed by a central reader post-surgery and blinded reports will be sent back to the assessment site staff (excluding the assessment site efficacy assessor) without any

	accompanying images. Exploratory imaging (e.g. diffusion tensor imaging [DTI] and dynamic susceptibility contrast [DSC] MRI for perfusion imaging) will also be performed at capable sites. Primary and secondary efficacy assessments will be completed solely by blinded study personnel that do not have access to patient study safety information (this includes adverse events, concomitant medications, progress notes, and MRI reports). Stopping Rules: If the DSMB determines that continuation of enrollment in the trial provides an unreasonable risk to the patients, it may recommend study termination. All SAEs, regardless of attribution shall be reviewed 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.
Patient Population	Adult patients with chronic motor deficits secondary to ischemic stroke between 6 months and 90 months (7.5 years) post stroke. The interval of 6 months to 90 months (7.5 years) 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. A Phase 1/2a study (SB-STR01) was conducted to investigate safety and efficacy of intracranial administration of SB623 cells in chronic stroke patients with motor deficit.
No. of Patients	Approximately 156 subjects
No. of Study Sites	Approximately 65 sites
Inclusion Criteria	1. Age 18-75 years, inclusive 2. Documented history of completed ischemic stroke in subcortical region of MCA or lenticulostriate artery with or without cortical involvement, with correlated findings by MRI 3. Between 6 months and 90 months (7.5 years) post-stroke, and having a chronic motor neurological deficit 4. Neurological motor deficit substantially due to incident stroke (ie, the stroke that qualified the patient for the study) 5. Modified Rankin Score of 2-4 6. Require Motricity Index 30-75 (UE Scale) or 27-74 (LE Scale) 7. Able to undergo all planned neurological assessments 8. Able and willing to undergo magnetic resonance imaging (MRI) with contrast and computed tomography (CT) 9. Agree that use of antiplatelet, anti-coagulant, or non-steroidal anti-inflammatory drugs be in accordance with the Anticoagulant Guidelines described in Appendix C. 10. Subjects must have had physical therapy prior to entry and be willing to continue to the extent possible 11. Must be willing to discontinue herbal or non-traditional medicines for 1 week before and 1 week after the surgical procedure 12. Ability of patient to understand and sign an Informed Consent
Exclusion Criteria	1. History or presence of any other major neurological disease other than stroke 2. Cerebral infarct size >150 cm^3 measured by MRI

	3. Primary intracerebral hemorrhage 4. Myocardial infarction within prior 6 mos. 5. Malignancy unless in remission >5 yrs. 6. Clinically significant finding on MRI of brain not related to stroke 7. Any seizures in the 3 months prior to Screening 8. More than 5 degrees of contracture at shoulder, elbow, wrist, fingers, hip, knee and ankle 9. Other neurologic, neuromuscular or orthopedic disease that limits motor function 10. Uncontrolled systemic illness, including, but not limited to: hypertension; diabetes; renal, hepatic, or cardiac failure 11. Positive findings on tests for occult malignancy, unless a non-malignant etiology is confirmed 12. Uncontrolled major psychiatric illness, including depression symptoms (CESD-R Scale of ≥16 is exclusionary) 13. Total bilirubin >1.9 mg/dL at Screening 14. Serum creatinine >1.5 mg/dL at Screening 15. Hemoglobin <10.0 g/dL at Screening 16. Absolute neutrophil count <2000 /mm^3 at Screening 17. Absolute lymphocytes <800 /mm^3 at Screening 18. Platelet count <100,000 /mm^3 at Screening 19. Liver disease supported by AST (SGOT) or ALT (SGPT) ≥2.5 x upper limit of normal at Screening 20. Serum calcium >11.5 mg/dL at Screening 21. International Normalized Ratio of Prothrombin Time (INR) >1.2 at Screening, if the patient does not take anticoagulants; for patients on anticoagulants, INR must be confirmed to be ≤1.2 prior to surgery 22. Presence of craniectomy (without bone flap replacement) or other contraindication to stereotactic surgery 23. Participation in any other investigational trial within 4 weeks of initial screening and within 7 weeks of Baseline visit 24. Botulinum toxin injection, phenol injection, intrathecal baclofen, or any other interventional treatments for spasticity (except bracing and splinting) 16 weeks prior to the Baseline visit 25. Substance use disorder (per DSM-V criteria, including drug or alcohol) 26. Contraindications to head MRI (with contrast) or CT 27. Pregnant or lactating 28. Female patients of childbearing potential unwilling to use an adequate birth control method during the 12 months of the study 29. 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 30. Any prior SB623 cell implantation and/or any prior stem cell treatment for stroke or other reason regardless of mode of administration 31. Subject is taking any prohibited medications (see Section 12.0)

Dosage, Mode of Administration, and Treatment Duration	The investigational product, SB623 cells, are sterile cell suspension in unit volume of 1 mL, containing ≥8 X 10^6 cells/mL, cryopreserved in CryoStore™ freezing media in a 2 mL vial. Cells to be administered stereotactically only once 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): • Approximately 2.5 X 10^6 SB623 Cells (8.5 X 10^6 cells/mL) • Approximately 5.0 X 10^6 SB623 Cells (17 X 10^6 cells/mL) Details for preparation of the cell suspension for administration and for loading the syringe in the Operation Room will be provided by the Sponsor to the clinical site unblinded personnel who will performed the cell target concentration preparation, labeling, administration and accountability of investigational product. Detailed information will be provided separately from this protocol in a Pharmacy Manual. Clinical sites will be provided with the 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 to achieve target concentrations of approximately 2.5 X 10^6 cells/ 0.3 mL and approximately 5 X 10^6 cells/ 0.3 mL, respectively. The formulated dose for injection is packaged individually in 1.0 mL conical Nalgene™ vials with a Teflon seal closure. 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 for release of target concentrations. The formulated dose for injection must be administered to the patient ***within 3 hours*** post release testing. 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. The cryovials containing the frozen cell suspensions are shipped in a dry nitrogen shipper and should be stored in the vapor phase (≤ -150 C) within the shipping container provided by the Sponsor until transferred at the site to a GMP-compliant liquid nitrogen container. At the clinical site, the investigational product should be stored in the vapor phase (≤ -150 C) within the liquid nitrogen container.
Duration of Patient Study Participation	Twelve months post-randomization (except if there is an unresolved adverse event of at least Grade 2 and at least possibly related to the therapy, in which case the patient will be followed until resolved or reduced to Grade 1).

Efficacy Parameters	**Primary Efficacy Endpoint:** • Proportion of subjects whose Fugl-Meyer Motor scale (FMMS) improve by ≥10 points at Month 6 from Baseline **Secondary Efficacy Endpoints:** • Proportion of subjects whose Modified Rankin Scale (mRS) improve by ≥1 point at Month 6 from Baseline • Proportion of subjects whose Action Research Arm Test (ARAT) improve by ≥6 points at Month 6 from Baseline • Proportion of subjects whose Gait Velocity on standard 10 m walk improve at least one functional level [eg, from <0.4 m/s to 0.4-0.8 m/s or from 0.4 - 0.8 m/s to >0.8 m/s]) at Month 6 from Baseline • Mean change in T scores at Month 6 of NeuroQOL sub-domains: o Upper Extremity Function (Fine motor ADL) o Lower Extremity Function (Mobility) • Proportion of subjects scoring 7 (much better) or 6 (a little improved) in the Global Rating of Perceived Change scores at Month 6 assessed by subject (may be completed by caregiver) and by clinician
Safety Parameters	• All adverse events whether or not related to SB623 or surgical procedure using WHO toxicity criteria • Adverse changes imaged by head MRI • Serious adverse events (SAEs) using WHO toxicity criteria • Serum chemistry, hematology, vital signs, physical examinations • Changes in serum antibodies to SB623 over time
Exploratory	• Standard T1- and T2-weighted MRI • Fluid-attenuated Inversion Recovery (FLAIR) • Dynamic Susceptibility Contrast (DSC) imaging • Diffusion tensor imaging (DTI) with tractography and perfusion imaging • Motion of leg on side affected by stroke as measured by leg activity monitor

Statistical Methods	**Sample Size:** The sample size was estimated based on the primary efficacy endpoint, proportion of responders, which is defined as ≥10 points on the FMMS, at Month 6 LOCF (last observation carried forward). Based on the results on the Phase 1/2a study it was assumed that the responder rate was 33% for the SB623 treatment group. Given high surgical placebo response rates (Meissner et al., 2013) it was assumed that the responder rate in the surgical sham was 11.7% (i.e. 35% of the treatment responder rate). Assuming a 80% power, alpha level of 0.05 (two-tailed test), and 2:1 (pooled SB623 treatments:control) ratio of randomization, a sample size of 138 (92 subjects in treatment group and 46 subjects in control group) is required to detect this 21.3% difference in the proportion of responders. Based on a 10% upward adjustment to compensate for dropout patients, a total of approximately 156 subjects (104 treatment and 52 control) will be required. **Primary Efficacy Analyses:** The primary analysis will be a comparison of the proportion of SB623 treated subjects (two SB623 doses combined) to sham controls that achieve an improvement of at least 10 points on the Fugl-Meyer Motor Scale at 6 months from Baseline. A logistic generalized linear mixed model (GLMM) will be used for the primary analysis. **Secondary Efficacy Analyses** The responder analysis in mRS and other disability scales will be assessed similarly to the model utilized for the primary analysis.

2.0 BACKGROUND

2.1 Medical Need

Stroke is the third leading cause of death in the United States and a major cause of prolonged neurologic disability in adults, with an annual economic burden of over $62 billion in the United States. Of those who experience an ischemic stroke, approximately one quarter will not survive. Of the survivors, more than a third will remain functionally dependent due to their physical and cognitive limitations.[1,2,3,4,5,6,7,8]

Following an ischemic stroke the acute period is generally defined from hours to several days following the event. 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 with current standard of care.[9] This time period was found to be independent of degree of initial severity regardless of methods used to assess by most investigators,[10,11] 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.[12]

Approximately 70–85% of first strokes are accompanied by hemiplegia. Six months after stroke, only 60% of people with hemiparesis who need inpatient rehabilitation have achieved functional independence in simple activities of daily living such as toileting and walking short distances. Studies of patients 6 months after stroke with hemiparesis suggest that only about 1 in 5 patients achieve unlimited community ambulation following inpatient rehabilitation.[13]

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.[14] 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.[15] 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.[16]

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.[17,18,19] 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,[20,21] and in an animal model of middle-cerebral artery occlusion[22] 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.[19]

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[23] were studied in an open-label Phase 1 clinical trial.[24,] 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.[25] 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%).[26] Further, a Phase 1/2a study with SB623 has been completed with all subjects followed through 24 months post-infarct. During this study there were serious adverse events attributed to the surgery, including subdural hematoma, hygroma, seizure disorder, and pneumonia.

2.3 Properties of SB623

2.3.1 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 cGMP conditions by the transient transfection of bone marrow stromal cells

(MASC) with a plasmid encoding the human Notch-1 intracellular domain.[27] 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.

2.3.2 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.

2.3.3 *Preclinical Pharmacology Studies*

SB623 has been evaluated in a rat model of ischemic stroke in three studies. Overall, SB623 showed statistically-significant benefit on several neurological and motor outcomes compared to vehicle control.

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.

Several studies evaluating the pharmacology and toxicology of SB623 cells (cell dosage, pharmacokinetics, formulation, efficacy, safety, biodistribution, tumorigenicity and use with cyclosporine) have been conducted. See the Investigator's Drug Brochure for details on these studies.

3.3 Clinical Experience

A 2-year Phase 1/2a study (SB-STR01 - NCT01287936) to investigate the safety and efficacy of intracranial administration of SB623 cells in chronic stroke patients with motor deficit has been completed. This was an open-label study of 18 chronic ischemic stroke patients who were shown to be stable in the 3 weeks prior to enrollment. The dose levels used were in a standard dose escalation paradigm: approximately 2.5M, 5.0M, and 10.0M cells administered once into the peri-infarct region of the brain. Four stroke measurement scales were used: NIHSS, ESS, F-M, and mRS. All of these scales, except mRS, showed a statistically-significant average improvement over Baseline at 6 months and other time points. For example, the average change from Baseline in the F-M scale was found to be 22 at six months (see Figures 1-3 below). The F-M scale is considered sensitive to improvements in motor function in stroke patients. Page, *et al*. (2012) evaluated the clinically important difference in the Upper Extremity F-M (UE F-M) to range from 4.25 to 7.25 points based on a study of 146 patients with chronic stroke.[28] The average change from Baseline in the UE F-M in SB-STR01 was 5.94 and therefore in the range of clinically important difference as defined by Page *et al*. Page, *et al.* also discusses a clinically important difference in the context of 10% improvement over the scale range. The average improvement score on the F-M scale in SB-STR01 was 22.19 points which is a 10% improvement over the 226 point F-M scale range and a 16% increase over baseline. Therefore, clinically relevant improvements have been demonstrated by 6 months post treatment.

The mRS scale did not show statistical or clinically meaningful change from baseline. Two subjects had an improvement of 1, and 1 subject had a 1 point worsening. Others were unchanged during the course of the study.

Both the NIHSS and the ESS were originally developed as predictors of acute stroke outcome.[29,30] They were both also used in the Phase 1/2a study due to their common use in acute stroke in the U.S. and Europe, respectively. See figures below.

Figure 1: ESS

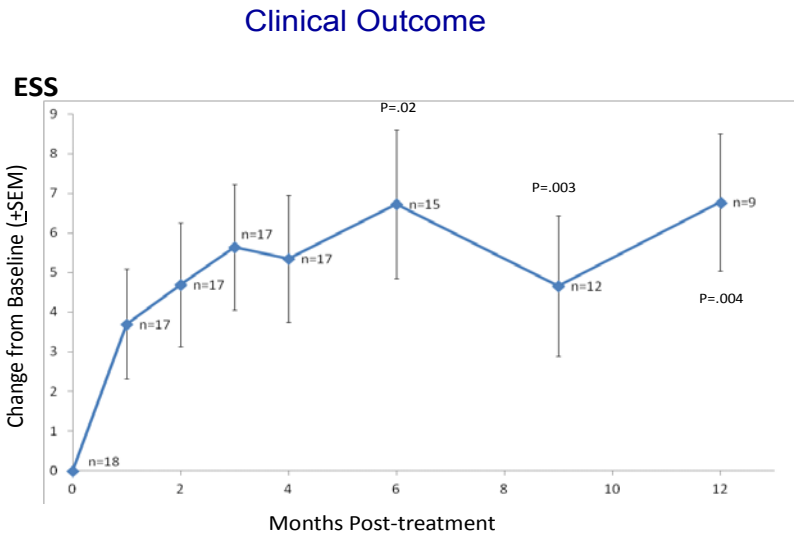


Figure 2: NIHSS

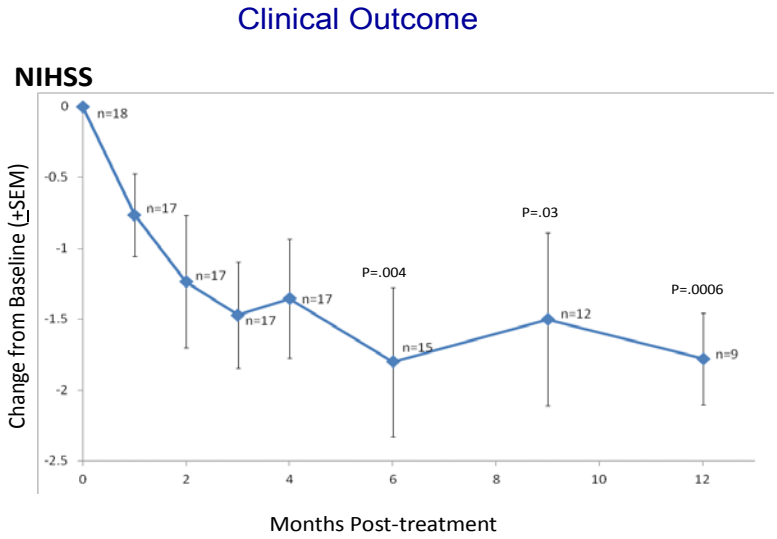
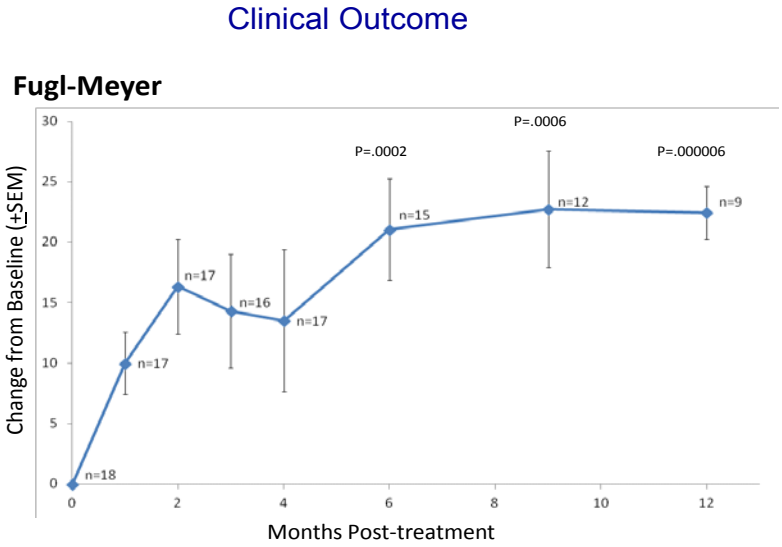


Figure 3: Fugl-Meyer



3.4 Summary of Known and Potential Risks and Benefits

A Phase 1/2a study (NCT01287936) in chronic stroke patients with motor deficit has been completed. There was a common theme of headache and local pain post-surgical procedure, but these were mild and transient. There were no serious adverse events attributable to SB623. All of the SAEs observed to date (six months post implant of the last patient) are summarized in Table 1 below.

Table 1: Summary of SAEs from SB-STR01 Study

Subject	Event	Grade	Attribution Cells	Attribution Surgery	Reason for SAE
01-006	Seizure Disorder	4	Unrelated	Possibly Related	Hospitalization
01-007	Subacute Subdural Hematoma (with Hygroma below)	3	Unrelated	Definitely Related	Hospitalization
01-007	Hygroma	3	Unrelated	Definitely Related	Hospitalization
01-012	UTI	4	Unrelated	Unrelated	Hospitalization
02-001	ICA Stenosis	3	Unrelated	Unrelated	Hospitalization
02-003	Recurrence of Stroke Symptoms	1	Unlikely Related	Unrelated	Hospitalization
02-006	Pneumonia	3	Unrelated	Probably Related	Hospitalization

No safety concerns with SB623 have been found. The Adverse Events attributed to SB623 have been Grade 3 or less, with attributions no higher than Possibly Related.

4.0 DESCRIPTION AND JUSTIFICATION OF TREATMENT REGIMEN

4.1 Dosages

Cells are to be administered stereotactically through one burr-hole craniostomy using 3 needle tracks adjacent to the infarct and 5 cell deposits per track at varying depths, with 20 µL per deposit.

Based on the 6-mo. follow-up data from SB-STR01, there was no apparent dose response in either safety or efficacy measures. Also, all doses were well tolerated. The dose of 10.0 million cells was associated with higher viscosity, making syringe-loading more difficult. Therefore, the two types of doses chosen for this Phase 2b study are approximately 2.5 and approximately 5.0 million cells. See Table 2 below.

Table 2: Dose, Volume and Cell Concentration

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
~2.5 X 10^6	1.7 X 10^5	8.5 X 10^5	8.5 X 10^6 cells/mL	20 µL, 100 µL, and 300 µL
~5.0 X 10^6	3.3 X 10^5	16.5 X 10^5	17 X 10^6 cells/mL	20 µL, 100 µL, and 300 µL

4.2 Justification

Based on the Phase 1/2a study, SB-STR01, no safety concerns with SB623 were seen, but efficacy was suggested. Therefore, a double-blind, controlled Phase 2b study is justified using patients who are not as disabled (mRS 2-4). The primary efficacy endpoint will be the Fugl-Meyer Motor Score, with the following scales as secondary endpoints:

- Modified Rankin Scale
- Action Research Arm Test
- Gait Velocity
- NeuroQOL (Upper Extremity Function and Lower Extremity Function)
- Global Rating of Perceived Change:
    - By Subject (The subject global rating of perceived change should be completed by the subject. In the event the subject is not able to complete the questionnaire, the caregiver will be allowed to ask the questions of the subject and complete the questionnaire using the subject's answer(s))
    - By Clinician

Rationales for selecting study endpoints are provided in Appendix A.

5.0 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 ischemic stroke.

5.1 Parameters

5.1.1 Primary Efficacy Endpoint:

- Proportion of subjects whose Fugl-Meyer Motor scale (FMMS) improve by ≥10 points at Month 6 from Baseline

5.1.2 Secondary Efficacy Endpoints:

- Proportion of subjects whose Modified Rankin Scale (mRS) improve by ≥1 point at Month 6 from Baseline
- Proportion of subjects whose Action Research Arm Test (ARAT) improve by ≥6 points at Month 6 from Baseline
- Proportion of subjects whose Gait Velocity on standard 10 m walk improve at least one functional level [eg, from < 0.4 m/s to 0.4-0.8 m/s or from 0.4 - 0.8 m/s to >0.8 m/s]) at Month 6 from Baseline
- Mean change in T scores at Month 6 of NeuroQOL sub-domains
  - Upper Extremity Function (Fine motor ADL)
  - Lower Extremity Function (Mobility)
- Proportion of subjects scoring 7 (much better) or 6 (a little improved) in the Global Rating of Perceived Change scores at Month 6 assessed by subject (may be completed by caregiver) and by clinician

5.1.3 Safety Endpoints

- All adverse events whether or not related to SB623 or surgical procedure using WHO toxicity criteria
- Adverse changes imaged by head MRI
- Serious adverse events (SAEs) using WHO toxicity criteria
- Serum chemistry hematology, vital signs, physical examinations
- Changes in serum antibodies to SB623 over time

5.1.4 Exploratory Endpoints

- Standard T1- and T2-weighted MRI
- Fluid-attenuated Inversion Recovery (FLAIR)
- Dynamic Susceptibility Contrast (DSC) imaging
- Diffusion tensor imaging (DTI) with tractography and perfusion imaging
- Motion of leg on side affected by stroke as measured by leg activity monitor

5.2 Objectives

5.2.1 Primary Objective

- To evaluate the clinical efficacy of intracranial administration of SB623 cells

5.2.2 Secondary Objectives

- To evaluate the effect of intracranial administration of SB623 cells on disability parameters
- To evaluate the safety and tolerability of intracranial administration of SB623 cells

6.0 SURGICAL AND IMPLANTATION PROCEDURES

The surgical procedure is a modification of one used earlier with another cell product,[25] 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.[26] This procedure was also used in the ongoing clinical trial SB-STR01. Two cohorts, Group 1 (2.5 and 5 million SB623 cells combined) and Group 2 (sham placebo), will be included in this study. Subjects who are randomized into this study will receive either approximately 2.5 million SB623 cells, approximately 5 million SB623 cells or sham surgery at a 1:1:1 randomization ratio. On the morning of surgery, 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 at least 1.5 tesla. Implant sites are to be determined in the subcortical peri-infarct tissue to surround the infarct. Three needle tracks are to be determined with trajectories to surround the infarct, so that cell deposit targets are spaced 5-6 mm apart. Either frameless or frame stereotaxy procedures may be used.

Group 1

One burr-hole craniostomy (1-1.5 cm) is to be fashioned under local anesthesia and sedation. The aim of the sedation is two-fold: to minimize subject discomfort and to prevent any subject recall or awareness of the procedure to preserve subject blinding. The dura is to be opened and a stabilizing cannula (size dependent on the use of a frame or frameless procedure) 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 an implantation cannula (previously qualified for product stability and delivery and provided by the Sponsor, as needed) down to the deepest target point for the first implantation. A safe trajectory to enter a 100 µL of cell suspension is defined. A volume of 125 µL of cells is backloaded into a 100 µL syringe, 25 µL of these cells are injected to clear the implant cannula, thus the final volume in the syringe for implant is 100 µL. Detailed information will be provided separately from this protocol in an Investigational Product Manual. 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 to produce equally spaced implants (intervals of 5-6 mm) within the peri-infarct region extending from inferior to the infarct to superior to the infarct. The target locations will be selected by the site neurosurgeon 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.

Group 2

Group 2 will receive sham surgery (sedation, stereotactic planning procedure, partial-thickness skull outer table burr hole, scalp suture, but no penetration of inner table or dura mater). This will be done under sedation and local anesthetic. Again the purpose of the sedation is two-fold: to minimize subject discomfort and to prevent any subject recall or awareness of the procedure to preserve subject blinding. The sham surgery procedure will be scripted to mimic as closely as possible the procedure undertaken by Group 1. Subjects in Group 2 will remain in the operating room for the same duration as Group 1.

Post-Surgical

After completion of the procedure, both groups will receive a CT scan and be admitted to a neurosurgical patient ward for 24 hour observation. 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 prior to discharge (ie, Day 2) to insure there are no significant bleeding risks.

7.0 PATIENT SELECTION

7.1 Inclusion Criteria

1. Age 18-75 years, inclusive
2. Documented history of completed ischemic stroke in subcortical region of MCA or lenticulostriate artery with or without cortical involvement, with correlated findings by MRI
3. Between 6 months and 90 months (7.5 years) post-stroke, and having a chronic motor neurological deficit
4. Neurological motor deficit substantially due to incident stroke (i.e. the stroke that qualified the patient for the study)
5. Modified Rankin Score of 2-4
6. Require Motricity Index 30-75 (UE Scale) or 27-74 (LE Scale)
7. Able to undergo all planned neurological assessments
8. Able and willing to undergo magnetic resonance imaging (MRI) with contrast and computed tomography (CT)
9. Agree that use of antiplatelet, anti-coagulant, or non-steroidal anti-inflammatory drugs be in accordance with the Anticoagulant Guidelines described in Appendix C
10. Subjects must have had physical therapy prior to entry (and be willing to continue to the extent possible)
11. Must be willing to discontinue herbal or non-traditional medicines for 1 week before and 1 week after the surgical procedure.
12. Ability of patient to understand and sign an Informed Consent

7.2 Exclusion Criteria

1. History or presence of any other major neurological disease other than stroke
2. Cerebral infarct size >150 cm^3 measured by MRI
3. Primary intracerebral hemorrhage
4. Myocardial infarction within prior 6 mos.
5. Malignancy unless in remission >5 yrs.
6. Clinically significant finding on MRI of brain not related to stroke
7. Any seizures in the 3 months prior to Screening
8. More than 5 degrees of contracture at shoulder, elbow, wrist, fingers, hip, knee and ankle
9. Other neurologic, neuromuscular or orthopedic disease that limits motor function
10. Uncontrolled systemic illness, including, but not limited to: hypertension; diabetes; renal, hepatic, or cardiac failure
11. Positive findings on tests for occult malignancy, unless a non-malignant etiology is confirmed
12. Uncontrolled major psychiatric illness, including depression symptoms (CESD-R Scale of ≥16 is exclusionary)
13. Total bilirubin >1.9 mg/dL at Screening

14. Serum creatinine >1.5 mg/dL at Screening
15. Hemoglobin <10.0 g/dL at Screening
16. Absolute neutrophil count <2000 /mm^3 at Screening
17. Absolute lymphocytes <800 /mm^3 at Screening
18. Platelet count <100,000 /mm^3 at Screening
19. Liver disease supported by AST (SGOT) or ALT (SGPT) ≥2.5 x upper limit of normal at Screening
20. Serum calcium >11.5 mg/dL at Screening
21. International Normalized Ratio of Prothrombin Time (INR) >1.2 at Screening, if the patient does not take anticoagulants; for patients on anticoagulants, INR must be confirmed to be ≤1.2 prior to surgery
22. Presence of craniectomy (without bone flap replacement) or other contraindication to stereotactic surgery
23. Participation in any other investigational trial within 4 weeks of initial screening and within 7 weeks of Baseline visit
24. Botulinum toxin injection, phenol injection, intrathecal baclofen, or any other interventional treatments for spasticity (except bracing and splinting) within 16 weeks of the Baseline visit.
25. Substance use disorder (per DSM-V criteria, including drug or alcohol)
26. Contraindications to head MRI (with contrast) or CT
27. Pregnant or lactating
28. Female patients of childbearing potential unwilling to use an adequate birth control method during the 12 months of the study
29. 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
30. Any prior SB623 cell implantation and/or any prior stem cell treatment for stroke or other reason regardless of mode of administration
31. Subject is taking any prohibited medications (see Section 12.0)

8.0 INVESTIGATIONAL PLAN

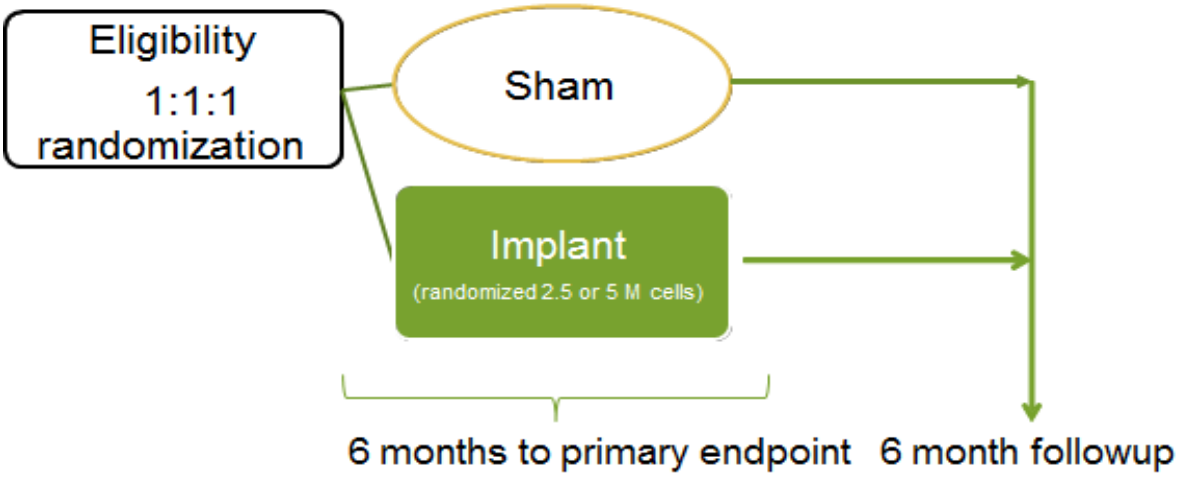
8.1 Overall Study Design

This is a double-blind, sham-surgery controlled study of stereotactic, intracranial injection of SB623 cells in patients with fixed motor deficits from ischemic stroke. The study will be conducted at approximately 65 sites in the United States.

Two cohorts, Group 1 (approximately 2.5 and approximately 5 million SB623 cells combined) and Group 2 (sham placebo), will be included in this study. Subjects who are randomized into this study will receive either approximately 2.5 million SB623 cells, approximately 5 million SB623 cells or sham surgery at a 1:1:1 randomization ratio. Randomization will be performed via an interactive web/voice response system (IXRS), stratified by Screening mRS score (recorded in the IXRS at the clinical site).

The study schematic is shown in the following figure.

Figure 4: Study Schematic



Note: Group 1 (Implant) will receive either approximately 2.5 million SB623 cells or approximately 5 million SB623 cells.
Abbreviation: M = million.

The neurological assessment team evaluating Fugl-Meyer and other efficacy endpoints will be blinded, with the subjects also blinded. The surgical team will remain unblinded, any communication between the surgical and neurological team (including the investigator) will be blinded.

Safety will be monitored throughout the study. In addition, an external Data Safety Monitoring Board will be utilized to review safety data, including clinical symptoms, laboratory findings, and MRI brain imaging. Two or more serious adverse events potentially attributed to SB623 as assessed by the Investigator will trigger a review by the DSMB before continuing enrollment. In addition, the DSMB will review the study for safety at 25%, 50%, and 75% enrollment. The DSMB shall be the final arbitrator for attributions.

Efficacy will be determined based on changes in the clinical measures of stroke through standardized assessments (Fugl-Meyer Motor Scale (FMMS), Modified Rankin Scale (mRS), Action Research Arm Test (ARAT), Gait Velocity and two sub-domains of the NeuroQOL scale). MRI of the brain will be performed at scheduled time points (pre- and post-contrast T1 weighted, dual echo, and FLAIR sequences). MRIs will be analyzed by a central reader post-surgery and blinded reports will be sent back to the assessment site staff (excluding the assessment site efficacy assessor) without any accompanying images. Exploratory imaging (e.g. diffusion tensor imaging [DTI] and dynamic susceptibility contrast [DSC] MRI for perfusion imaging) will also be performed at capable sites.

The primary and secondary efficacy assessments will be completed solely by blinded study personnel that do not have access to patient study safety information (this includes adverse events, concomitant medications, progress notes, and MRI reports).

Stopping Rules:

If the DSMB determines that continuation of enrollment in the trial provides an unreasonable risk to the patients, it may recommend study termination. All SAEs, regardless of attribution shall be reviewed 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.

8.2 Duration of Patient Participation

Twelve months post-surgery (except if there is an unresolved adverse event of at least Grade 2 and at least possibly related to the therapy, in which case the patient will be followed until resolved or reduced to Grade 1).

9.0 STUDY ASSESSMENTS

9.1 Schedule of Study Activities

Table 3 below lists the procedures to be followed throughout the course of the study.

Table 3: Schedule of Assessments

Study Period	**Screening**	**Baseline**	**Sham or Cell Admin**		**Follow-Up Period**				
Study Visit Type	**Assessment**	**Assessment**	**Surgical**		**Assessment**				
Study Visit	**1**	**2**	**3A**[1]	**3B**	**4**	**5**	**6**	**7**	**8**
Study Day	**-84 to -22**	**-21 to -2**	**-1**	**1**	**2**	**8 (± 1)**	**28 (± 7)**	**84 (± 7)**	**168 (± 7)**
Study Week						**1**	**4**	**12**	**24**
Study Month							**1**	**3**	**6**
Informed Consent	X		X[2]						
Demographics	X								
Inclusion/Exclusion	X								
Eligibility Criteria Review[3]		X	X						
Randomization				X					
Medical History (including stroke history)	X								
Physical Therapy Instruction and Subject Exercise Diary given to subject	X					X	X	X	X
Subject Exercise Diary Review		X					X	X	X
Leg Activity Monitor given to subject	X	X				X	X	X	X
Collect Leg Activity Monitor		X				X	X	X	X
Pregnancy Test[4]	X	X	X						X
Physical Exam	X	X	X						X
Vital Signs (weight and height recorded at Screening only)	X	X	X	X		X	X	X	X
Chest X-Ray and ECG	X		X						X
Hematology	X		X[3]			X	X	X	X
Serum Chemistry	X		X[3]			X	X	X	X
INR	X		X[3]						X
HLA typing of each subject		X							
ApoE4 & BDNF Val66Met genotyping		X							
Serum for anti-HLA Antibodies[5]		X				X	X	X	X
PBMC Sample[5]		X				X	X	X	X
Occult Malignancy	X								
CESD-R Scale	X								
Head CT				X[6]					
Imaging--Head MRI[7]	X	X		X[8]	X	X	X		X
Motricity Index	X								

Study Period	**Screening**	**Baseline**	**Sham or Cell Admin**		**Follow-Up Period**				
Study Visit Type	**Assessment**	**Assessment**	**Surgical**		**Assessment**				
Study Visit	**1**	**2**	**3A[1]**	**3B**	**4**	**5**	**6**	**7**	**8**
Study Day	**-84 to -22**	**-21 to -2**	**-1**	**1**	**2**	**8 (± 1)**	**28 (± 7)**	**84 (± 7)**	**168 (± 7)**
Study Week						**1**	**4**	**12**	**24**
Study Month							**1**	**3**	**6**
Imaging – Diffusion Tensor Imaging[9]		X					X		X
Modified Rankin Score (mRS)[10]	X[11]	X					X	X	X
Fugl-Meyer Motor Score (FMMS)[10]		X					X	X	X
Action Research Arm Test (ARAT)[10]		X					X	X	X
Gait Velocity[10]		X					X	X	X
NeuroQOL (2 subdomains)[10]		X					X	X	X
Global Rating of Perceived Change (subject and clinician) – 7-point Likert Scale[10, 12]							X	X	X
Admission[1]			X						
Sham Surgery or Cell Administration[13]				X					
Discharge[14]					X				
Adverse Events[15]	X	X	X	X[16]	X	X	X	X	X
Concomitant Medications	X[17]	X	X	X[16]	X	X	X	X	X

1 Pre-operative procedures may be performed within 14 days of the surgery day and admission may occur on the day of surgery (Day 1) to accommodate scheduling.

2 Confirmation of appropriate Informed consent.

3 The assessment of a subject's suitability for surgery will be performed at Visit 3A (Day -1) according to clinical site standard practice and Investigator judgement.
NOTE: Hematology, Serum Chemistry, and INR at admission (Visit 3A) are to be performed by both the central laboratory (for data collection purposes) and the local laboratory (to ensure subject is suitable for surgical procedure), all other on study laboratory assessments to be done by central laboratory only.
NOTE: Post-operative visits may be conducted according to the surgical site's standard of care.

4 Only for women of childbearing potential. Serum β-HCG at Screening (Visit 1), Visit 8, and Visit 10; either serum or urine β-HCG at Baseline (Visit 2) and Admission (Visit 3A).

5 At each timepoint that serum antibody samples are collected an additional sample for PBMC will also be collected and stored at the central laboratory.

6 Head CT on Day 1 is post-operative.

7 Magnetic Resonance Imaging (MRI) of the brain will be obtained using either a 1.5 or 3 Tesla MRI scanner. Each subject should have all scans conducted on the same scanner if possible (excepting those used for stereotactic planning and post-operative assessments, within 2 weeks of the surgery (implant/sham). Standard T1 and T2 sequences and FLAIR will be obtained, and will be recorded in standard digital format for review. Contrast is to be utilized for MRI procedures at Baseline (Visit 2), Day of surgery (Visit 3B), Day 8 (Visit 5), Month 1 (Visit 6), and Month 12 (Visit 10); at these visits

Dynamic Susceptibility Contrast (DSC) imaging will also be performed. All other scheduled MRI to be performed without contrast. MRI within 3 months of Visit 1 is acceptable for Screening MRI.

8 Or CT overlaid with MRI from Baseline. Contrast is not to be utilized for CT procedures.

9 Diffusion tensor imaging (DTI) is an MRI technique which characterizes the magnitude, anisotropy and orientation of the diffusion tensor, using the pulsed-gradient, spin echo pulse sequence with a single-shot, echo planar imaging readout. DTI data will be obtained using whole brain coverage, a maximum of 2.5 mm isotropic resolution and at least 30 diffusion encoding directions and may be obtained using either a 1.5 or 3 Tesla MRI scanner. DTI is required for subjects at assessment sites with DTI capability. DTI is optional for sites without access to DTI-compatible scanners. Perfusion imaging is also required for subjects at assessments sites when the MRI has the capacity.

10 All efficacy assessments will be completed solely by blinded study personnel that do not have access to patient study safety information (this includes adverse events, concomitant medications, progress notes, and MRI reports).

11 The mRS Screening value is to be recorded by the clinical site utilizing the IXRS.

12 The subject global rating of perceived change should be completed by the subject. In the event the subject is not able to complete the questionnaire, the caregiver will be allowed to ask the questions of the subject and complete the questionnaire using the subject's answer(s).

13 Subjects will undergo study surgical procedure on Day 1 only after all other procedures for this visit have been completed.

14 Subjects will be discharged on Day 2 unless complications require a longer stay.

15 Adverse event collection begins from the time Informed Consent is provided.

16 During the surgical visit, adverse events and concomitant medications will be recorded pre- and post-surgery.

17 Including prior and concomitant medications at Screening.

Table 3: Schedule of Assessments (Continued)

Study Period	**Follow-up**	
Study Visit Type	**Assessment**	
Study Visit	**9**	**10/ Early Termination**
Study Day	**252 (± 14)**	**336 (± 14)**
Study Week	**36**	**48**
Study Month	**9**	**12**
Pregnancy Test[1]		X
Physical Exam		X
Physical Therapy Instruction and Subject Exercise Diary given to subject	X	
Subject Exercise Diary Review	X	X
Leg Activity Monitor Given to Subject	X	
Leg Activity Monitor Collected from Subject	X	X
Vital Signs	X	X
Chest X-Ray and ECG		X
Hematology	X	X
Serum Chemistry	X	X
INR		X
Serum for anti-HLA Antibodies[2]		X
PBMC[2]		X
Imaging--Head MRI[3]		X
Imaging – Diffusion Tensor Imaging[4]		X
Modified Rankin Score (mRS)[5]	X	X
Fugl-Meyer Motor Score (FMMS)[5]	X	X
Action Research Arm Test (ARAT)[5]	X	X
Gait Velocity[5]	X	X
NeuroQOL (2 subdomains)[5]	X	X
Global Rating of Perceived Change (subject and clinician) – 7-point Likert Scale[5, 6]	X	X
Adverse Events	X	X
Concomitant Medications	X	X

1 Only for women of childbearing potential, Serum β-HCG.

2 At each timepoint that serum antibody samples are collected, an additional sample for PBMC will also be collected and stored at the central laboratory.

3 Magnetic Resonance Imaging (MRI) of the brain will be obtained using either a 1.5 or 3 Tesla MRI scanner. Each subject should have all scans conducted on the same scanner if possible (excepting those used for stereotactic planning and post-operative assessments, within 2 weeks of the surgery (implant/sham). Standard T1 and T2 sequences and FLAIR will be obtained, and will be recorded in standard digital format for review. Contrast is to be utilized for MRI procedures at Baseline (Visit 2), Day of surgery (Visit 3B), Day 8 (Visit 5), Month 1 (Visit 6), and Month 12 (Visit 10); at these visits, Dynamic Susceptibility Contrast (DSC) imaging will also be performed. All other scheduled MRI to be performed without contrast.

4 Diffusion tensor imaging (DTI) is an MRI technique which characterizes the magnitude, anisotropy and orientation of the diffusion tensor, using the pulsed-gradient, spin echo pulse sequence with a single-shot, echo planar imaging readout. DTI data will be obtained using whole brain coverage, a maximum of 2.5 mm isotropic resolution and at least 30 diffusion encoding directions and may be obtained using either a 1.5 or 3 Tesla MRI scanner. DTI is required for subjects at assessment sites with DTI capability. DTI is optional for sites without access to DTI-compatible scanners. Perfusion imaging is also required for subjects at assessments sites when the MRI has the capacity.

5 All efficacy assessments will be completed solely by blinded study personnel that do not have access to patient study safety information (this includes adverse events, concomitant medications, progress notes, and MRI reports).

6 The subject global rating of perceived change should be completed by the subject. In the event the subject is not able to complete the questionnaire, the caregiver will be allowed to ask the questions of the subject and complete the questionnaire using the subject's answer(s).

9.2 Pre-study Evaluation and Baseline

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.

9.2.1 Visit 1: Screening (Day -84 to -22; Assessment Site)

The Medical Monitor will be consulted if any screening procedures may be conducted outside the specified Screening visit window (eg, due to operating room scheduling delay).

- Inclusion/Exclusion Criteria (refer to Appendix C for anticoagulant guidelines)
- Demographics
- Medical History (including stroke history)
- Prior and concomitant Medications
- Pregnancy Test (serum β-hCG) for women of childbearing potential only
- Physical Therapy Instructions and Subject Exercise Diary given to subject
- Leg Activity Monitor Given to Subject
- Physical Exam
- Vital Signs Including Weight and Height
- Chest X-Ray
- 12-lead ECG
- Hematology
- Serum Chemistry
- INR
- Determination of occult malignancy
- CESD-R Scale Administration (subject must have score of <16)
- Imaging (head MRI). NOTE: MRI within 3 months of Visit 1 is acceptable for Screening MRI as long as meets criteria (does not require DTI or perfusion imaging)
- Clinical Stroke Evaluation (Modified Rankin and Motricity Index)
- Adverse events

Subjects may be re-screened with the approval of the medical monitor. If during the screening or re-screening period, there is a change in medical condition, additional, repeat, or unscheduled procedures may be performed at the Investigator's discretion.

9.3 Baseline and Confirmation of Eligibility

9.3.1 Visit 2: Baseline (Day -21 to -2; Assessment Site)

The following will be performed at Baseline:

- Eligibility Criteria Review
- Adverse events
- Concomitant medications
- Pregnancy Test (serum or urine β-hCG) for women of childbearing potential only
- Physical Exam
- Subject Exercise Diary Review
- Collect Leg Activity Monitor
- Re-issue Leg Activity Monitor
- Vital Signs
- HLA typing (molecular) of each subject
- ApoE4 & BDNF Val66Met genotyping of each subject
- Blood draw for Serum anti-HLA Antibodies
- Blood draw for PBMC
- Imaging (head MRI)
- Exploratory Imaging (Standard T1- and T2-weighted MRI, and FLAIR), and at sites with capability Diffusion tensor imaging (DTI) with tractography and perfusion imaging (including DSC)
- Clinical Stroke Evaluations (FMMS; mRS; ARAT; Gait Velocity; NeuroQOL (Upper Extremity Function and Lower Extremity Function)

9.3.2 Eligibility Confirmation

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

9.4 Surgical Admission (Visit 3A: Day -1; Surgical Site)

Pre-operative procedures may be performed within 14 days of the surgery day and admission may occur on the day of surgery (D1) to accommodate scheduling.

- Admission
- Confirm Informed Consent
- Review Eligibility Criteria to determine suitability for surgery (according to clinical site standard practice and Investigator judgment)
- Adverse events
- Concomitant medications
- Pregnancy Test (serum or urine β-hCG) for women of childbearing potential only
- Physical Exam

- Vital Signs
- Chest X-ray
- 12-lead ECG
- Hematology
- Serum Chemistry
- INR

9.5 Randomization and Cell Administration or Sham Surgery (Visit 3B: Day 1; Surgical Site)

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

- Adverse events
- Concomitant medications
- Vital Signs
- Imaging (head MRI or CT with MRI overlay)
- Randomization

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

Group 1:

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.

Group 2:

Subjects will be given procedures similar to Group 1, except will be given a sham surgery (light sedation, stereotactic procedure, partial-thickness skull outer table burr hole, scalp suture, but no penetration of inner table or dura mater).

After cell implantation or sham surgery, the following will be performed:

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

9.6 Visit 4: Follow-Up Period (Study Day 2; Surgical Site)

The following will be performed at the surgical site:

- Adverse Events
- Concomitant Medications
- Head MRI
- Discharge

NOTE: If additional days are required in the clinic, adverse events and concomitant medications will be monitored and recorded. Post-operative visits may be scheduled as required by the site's standard of care.

9.7 Visit 5: Follow-Up Period (Week 1, Study Day 8 ± 1; Assessment Site)

The following will be performed:

- Adverse Events
- Concomitant Medications
- Vital Signs
- Hematology
- Serum Chemistry
- Physical Therapy Instructions and Subject Exercise Diary given to subject
- Collect Leg Activity Monitor
- Re-issue Leg Activity Monitor
- Blood draw for Serum anti-HLA Antibodies
- Blood draw for PBMC
- Head MRI (MRI must be read before re-starting any antiplatelet, anticoagulant, or non-steroidal anti-inflammatory agents)

9.8 Visit 6: Follow-Up Period (Month 1, Study Day 28 ± 7; Assessment Site)

- Adverse Events
- Concomitant Medications
- Vital Signs
- Hematology
- Serum Chemistry
- Blood draw for Serum anti-HLA Antibodies
- Blood draw for PBMC
- Subject Exercise Diary Review
- Physical Therapy Instructions and Subject Exercise Diary given to subject
- Collect Leg Activity Monitor

- Re-issue Leg Activity Monitor
- Imaging (head MRI)
- Exploratory Imaging (Standard T1- and T2-weighted MRI, and FLAIR), and at sites with capability Diffusion tensor imaging (DTI) with tractography and perfusion imaging (including DSC)
- Clinical Stroke Evaluations (FMMS; mRS; ARAT; Gait Velocity; NeuroQOL (Upper Extremity Function and Lower Extremity Function)
- Global Rating of Perceived Change: subject and clinician, 7-point Likert scale

9.9 Visit 7: Follow-Up Period (Month 3, Study Day 84 ± 7; Assessment Site)

- Adverse Events
- Concomitant Medications
- Vital Signs
- Hematology
- Serum Chemistry
- Blood draw for Serum anti-HLA Antibodies
- Blood draw for PBMC
- Subject Exercise Diary Review
- Physical Therapy Instructions and Subject Exercise Diary given to subject
- Collect Leg Activity Monitor
- Re-issue Leg Activity Monitor
- Clinical Stroke Evaluations (FMMS; mRS; ARAT; Gait Velocity; NeuroQOL (Upper Extremity Function and Lower Extremity Function)
- Global Rating of Perceived Change: subject and clinician, 7-point Likert scale

9.10 Visit 8: Follow-Up Period (Month 6, Study Day 168 ± 7; Assessment Site)

- Adverse Events
- Concomitant Medications
- Pregnancy test (serum β-hCG) for women of childbearing potential only
- Physical Exam
- Subject Exercise Diary Review
- Physical Therapy Instructions and Subject Exercise Diary given to subject
- Collect Leg Activity Monitor
- Re-issue Leg Activity Monitor
- Vital Signs

- Chest X-ray
- 12-lead ECG
- Hematology
- Serum Chemistry
- INR
- Blood draw for Serum anti-HLA Antibodies
- Blood draw for PBMC
- Imaging (head MRI)
- Exploratory Imaging (Standard T1- and T2-weighted MRI, and FLAIR), and at sites with capability Diffusion tensor imaging (DTI) with tractography and perfusion imaging (including DSC)
- Clinical Stroke Evaluations (FMMS; mRS; ARAT; Gait Velocity; NeuroQOL (Upper Extremity Function and Lower Extremity Function)
- Global Rating of Perceived Change: subject and clinician, 7-point Likert scale

9.11 Visit 9: Follow-Up Period (Month 9, Study Day 252 ± 14; Assessment Site)

- Adverse Events
- Concomitant Medications
- Vital Signs
- Hematology
- Serum Chemistry
- Subject Exercise Diary Review
- Physical Therapy Instructions and Subject Exercise Diary given to subject
- Collect Leg Activity Monitor
- Re-issue Leg Activity Monitor
- Clinical Stroke Evaluations (FMMS; mRS; ARAT; Gait Velocity; NeuroQOL (Upper Extremity Function and Lower Extremity Function)
- Global Rating of Perceived Change: subject and clinician, 7-point Likert scale

9.12 Visit 10/Early Termination: Follow-Up Period (Month 12, Study Day 336 ± 14; Assessment Site)

- Adverse Events
- Concomitant Medications
- Pregnancy test (serum β-hCG) for women of childbearing potential only
- Serum Chemistry

- Subject Exercise Diary Review
- Collect Leg Activity Monitor
- Vital Signs
- Chest X-ray
- 12-lead ECG
- Hematology
- Serum Chemistry
- INR
- Blood draw for Serum anti-HLA Antibodies
- Blood draw for PBMC
- Imaging (head MRI)
- Exploratory Imaging (Standard T1- and T2-weighted MRI, and FLAIR), and at sites with capability Diffusion tensor imaging (DTI) with tractography and perfusion imaging (including DSC)
- Clinical Stroke Evaluations (FMMS; mRS; ARAT; Gait Velocity; NeuroQOL (Upper Extremity Function and Lower Extremity Function)
- Global Rating of Perceived Change: subject and clinician, 7-point Likert scale

10.0 DESCRIPTION OF STUDY TREATMENT

10.1 Study Product Description

The investigational product, SB623 cells, are sterile cell suspension in unit volume of 1 mL, containing ≥8 X 10^6 cells/mL, cryopreserved in CryoStore™ freezing media in a 2 mL vial.

10.2 Study Product Packaging and Labeling

The investigational product, SB623 cells, are provided to clinical sites in unit volume of 1 mL suspension, packaged and cryopreserved in CryoStore™ freezing media in a 2 mL Nalgene™ cryovials with a Teflon® seal closure. The vials are labeled at minimum with the following information:

- Product Name (SB623)
- Manufacture Lot. Number
- Vial number
- Sponsor Name and Address
- Manufacturer Name and Address
- Storage Conditions
- Investigational Drug Statement in accordance with 21CFR312.6

10.3 Study Product 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 (≤ -150 ^oC) within the shipping container provided by the Sponsor until transferred at the site to a GMP-compliant liquid nitrogen container. At the clinical site, the investigational product should be stored in the vapor phase (≤ -150 ^oC) within the liquid nitrogen container.

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

10.4 Preparation and Administration

Details for preparation of the cell suspension for administration and for loading the syringe in the Operation Room will be provided by the Sponsor to the clinical site unblinded personnel who will performed the cell target concentration preparation, labeling, administration and accountability of investigational product. Detailed information will be provided separately from this protocol in an Investigational Product Manual. Clinical sites will be provided with the 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 to achieve target concentrations of approximately 2.5 X 10^6 cells/ 0.3 mL and approximately 5 X 10^6 cells/ 0.3 mL, respectively. The formulated dose for injection is packaged individually in 1.0 mL conical Nalgene ™ vials with a Teflon seal closure.

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 for release of target concentrations.

The formulated dose for injection must be administered to the patient ***within 3 hours*** post release testing.

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.

10.5 Study Product Accountability Procedures

The Investigator will be responsible for maintaining inventory and accounting for all Study Product received from the Sponsor. The investigator will be responsible for the accountability of target concentrations prepared and actually used for dosing for a subject. After reconciliation has been completed, all unused Study Product vials received by the Investigator will be returned to the Sponsor in a dry nitrogen shipper stored in the vapor phase. All vials (used or unused [ie, resuspended cells]) are to be returned to the cell laboratory for reconciliation destruction.

11.0 TREATMENT ASSIGNMENT AND BLINDING

This is a double-blind study. Subjects will be randomized in a 1:1:1 ratio via an IXRS, stratified by Screening mRS score. Each subject will be randomized at a surgical site prior to the surgical procedure after study eligibility is confirmed. The randomization will be balanced, in terms of numbers of subjects between the treatment groups, within each surgical site.

The blind will be maintained by role definition and procedures described below:

Unblinded personnel:

- Cell preparation staff
- Unblinded study coordinator
- Surgeon and Operating Room staff
- Designated unblinded sponsor & clinical research organization (CRO) personnel
- Data and Safety Monitoring Board (DSMB) members and the supporting statistician and programmer involved in regular review and generation of unblinded safety data

Blinded personnel:

- Assessment site staff
- Designated blinded sponsor & CRO personnel

In order to maintain the blind the following procedures will be implemented:

1. Unblinded cell preparation staff will prepare and perform a quality check of the cell suspension for each subject. The identity of the treatment will be concealed by the preparation of study product that is identical in packaging, labeling, schedule of administration, administration, and appearance.
2. The neurosurgeon and Operating Room (OR) staff will perform the sham surgery procedure using a surgical script that mimics the cell administration procedure as closely as possible (e.g. sequence of steps and overall time taken in the OR).
3. Subjects, assessment site staff, persons performing the assessments, blinded sponsor staff, and blinded CRO staff will remain blind to the identity of the treatment from the time of randomization until database lock and unblinding, using the following methods:
    a. Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by any of the blinded study personnel in the study, unless subject level emergency unblinding is required as noted in section 11.1 Emergency Unblinding Procedures.
    b. MRIs will be analyzed by a central reader post-surgery and blinded reports will be sent back to the assessment site staff (excluding the Assessment site efficacy assessor) without any accompanying images. Description of the craniotomy skull defect and needle tract from the stereotactic surgical procedure are unblinding by definition and will therefore be excluded from the blinded head MRI reports. If an unscheduled head MRI is to be done, the same process shall be followed as for the scheduled head MRI scans to maintain blinding, unless a local read is necessary for clinical care per assessment site investigator's discretion. These unblinding events will be recorded and reported to the Sponsor.

c. To further safeguard maintenance of the blind, all efficacy assessments are to be completed solely by the efficacy assessors at assessment sites, who will be segregated from other activities at the assessment site and not have access to any patient study safety information (e.g. adverse events, concomitant medications, head imaging reports, and medical charts etc.).

d. All sites will be trained on Maintenance of the blind procedures and the training will be documented prior to site activation.

The following are the exceptions to those staff required to remain blinded: Data and Safety Monitoring Board (DSMB) members involved in regular review of safety data, unblinded cell preparation staff, unblinded neurosurgeon and OR surgical staff, unblinded study monitor.

11.1 Emergency Unblinding Procedures

The blinded treatment assignment/dose information is to be broken only in an emergency when knowledge of such treatment may have an impact on further treatment decisions or aid in the emergency treatment of the subject. The Investigator will obtain the treatment assignment for the specified subject by accessing the IXRS. Date and reason for unblinding are to be promptly communicated via telephone and in writing to the Medical Monitor and documented in the CRF.

Any subject for whom the treatment assignment/dose information was unblinded should continue to follow study procedures.

12.0 CONCOMITANT MEDICATIONS

The following medications should not be used during participation in the study:

- Bupropion (Wellbutrin®, Zyban®, others)
- Tricyclic Antidepressants (includes amitryptilene, nortryptilene, clomipramine, others)
- Clozapine (Clozaril®)
- Tramadol (Ultram®, Ultracet®)
- Meperidine (Demerol®)
- Theophylline (Theolair®, Slo-Bid®, Aminophylline, others)
- Cyclosporin

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 12 months post-Study Product (ie, End of Study) or Early Termination will be documented. Documentation 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.

Refer to Appendix C for anticoagulant guidelines.

13.0 STUDY WITHDRAWAL/TERMINATION

13.1 Study Termination

The protocol may be terminated at any time 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 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. If possible, the Investigator should attempt to evaluate the medical condition for 12 months post-surgery for any patient who has withdrawn (provided the patient consents to such follow-up).

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 or registered mail. Patients lost to follow up will still be included in the analysis of the study. For patients lost to follow up, the Investigator will be asked to check public records for survival status at 12 months when possible.

14.0 STOPPING RULES

If the DSMB determines that continuation of enrollment in the trial provides an unreasonable risk to the patients, it may recommend study termination. All SAEs, regardless of attribution shall be reviewed 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 (Including Stroke History)

Medical history (including stroke history) will include significant medical conditions and surgical history, medications taken within 2 weeks prior to 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 (while subject is in seated position), heart rate, and respiratory rate. Weight and height will be recorded at screening only.

15.3 Safety Laboratory

All safety laboratory evaluations will be conducted at a central laboratory (except at surgical visit). At every sampling time point, approximately 15 mL of blood will be drawn for each of the hematology and serum chemistry panels. Detailed information regarding collection of blood samples for clinical safety laboratory evaluations will be provided separately from this protocol.

The following laboratory evaluations will be performed:

- Hematology Panel: hematocrit, hemoglobin, WBC, platelet count, absolute lymphocyte count, absolute neutrophil count
- Serum Chemistry Panel: sodium, chloride, calcium, potassium, magnesium, creatinine, BUN, AST, ALT, alkaline phosphatase, and total bilirubin
- INR

15.4 Pregnancy Test: Serum or urine β-hCG

- Serum β-hCG at Screening (using same blood draw as for serum chemistry), Visit 8, and Visit 10
- Serum β-hCG or Urine β-hCG at Baseline and Admission (Visit 3A)

Detailed information regarding collection of samples for pregnancy testing will be provided separately from this protocol.

15.5 HLA typing and ApoE4 and BDNF Val66Met Genotyping

HLA typing (molecular) of each subject will be performed at baseline to allow exploratory analysis of degree of mismatch to SB623 with respect to both efficacy and safety.

Genotyping at the ApoE locus (ie, to determine if patient is homozygous for ApoE4, E2 or E3, or if patient is heterozygous for E2/E3, E3/E4 or E2/E4) will be performed at baseline.

Assessment of whether BDNFVal66Met mutation is present (yes/no) will be performed at baseline.

A central laboratory will be utilized for sample storage and assay. Detailed information regarding collection of samples will be provided separately from this protocol.

The samples will be stored for at least 15 years to allow for post marketing analysis.

15.6 Serum Anti-HLA Antibodies

Anti-HLA serum antibody measurements will be made to monitor a possible humoral-mediated immune response. Blood samples will be taken at the intervals indicated in the schedule of assessments for measurements of serum anti-HLA antibodies using the Luminex assay and for storage. Assays will be done periodically on pooled samples. A central laboratory will be utilized for sample storage and assay. Detailed information regarding collection of samples will be provided separately from this protocol.

The samples will be stored for at least 15 years to allow for post marketing analysis.

15.7 PBMC Samples

At each timepoint that serum antibody samples are collected, an additional sample for PBMC will also be collected. A central laboratory will be utilized for sample storage. Detailed information regarding collection of samples will be provided separately from this protocol.

The samples will be stored for at least 15 years to allow for post marketing analysis.

15.8 Occult Malignancy

Occult Malignancy will be determined 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.

15.9 CESD-R

The Center for Epidemiologic Studies Depression Scale Revised will be used for screening for depression and depressive disorder.

15.10 Clinical Stroke Evaluations

Detailed information regarding clinical stroke evaluations (including sample forms and instructions for conducting the evaluations) will be provided separately from this protocol.

Fugl-Meyer Motor Score (FMMS)

FMMS will be calculated as change from baseline for Months 1, 3, 6 (primary), 9 and 12. The treatment group will be compared to the control group based on the relative proportion of subjects who improve at least 10 points.

Modified Rankin Scale (mRS)

The mRS will be calculated to determine eligibility (mRS 2-4) at screening and again at Baseline, Months 1, 3, 6 (secondary), 9 and 12 months. The treatment group will be compared to the control group based on based on the relative proportion of subjects who improve at least

1 point. The mRS for all assessments except the Screening assessment will be recorded on video and reviewed in a blinded fashion by a central external rater.

Motricity Index

To ensure subjects have a defined motor deficit, an assessment of the subject's Motricity Index will be calculated at Screening for study eligibility purposes. Subjects will require either Motricity Index 30-75 (Upper Extremity Scale) OR 27-74 (Lower Extremity Scale).

Action Research Arm Test (ARAT)

ARAT scores will be calculated at Baseline and Months 1, 3, 6 (secondary), 9 and 12. The treatment group will be compared to the control group based on the relative proportion of subjects who improve at least 6 points.

Gait Velocity

Gait Velocity on a standard 10 m walk will be calculated at Baseline and Months 1, 3, 6 (secondary), 9 and 12. The treatment group will be compared to the control group based on the relative proportion of subjects who improve at least one functional level (e.g. from <0.4 m/s to 0.4-0.8 m/s or from 0.4-0.8 m/s to >0.8 m/s).

NeuroQOL

Two subdomains of the NeuroQOL will be assessed at Baseline and Months 1, 3, 6 (secondary), 9 and 12 using the Short Forms. The 2 subdomains include: Upper Extremity Function (Fine motor ADL) and Lower Extremity Function (Mobility). The treatment group will be compared to the control group based on the mean change in T Scores from baseline.

Global Rating of Perceived change from Baseline

This assessment will be performed at Months 1, 3, 6 (secondary), 9 and 12. It will be performed by both subject (may be completed by caregiver) and clinician. Subjects and clinicians will be asked about perceived changes in their motor function by comparing "how well they are doing compared to before the surgical procedure". The subject global rating of perceived change should be completed by the subject. In the event the subject is not able to complete the questionnaire, the caregiver will be allowed to ask the questions of the subject and complete the questionnaire using the subject's answer(s). The following 7-point Likert scale will be used:

- Score 7 = Much better
- Score 6 = A little better, meaningful
- Score 5 = A little better, not meaningful
- Score 4 = About the same
- Score 3 = A little worse, not meaningful
- Score 2 = A little worse, meaningful

- Score 1 = Much worse

15.11 Physiotherapy

Subjects will be instructed on of a set of exercises (cylinder grasp, thumb raise, stand and squat, walk) to be carried out at home every morning and afternoon while in the study. Subjects will be asked to keep a daily diary of their performance of the exercises.

Physical therapy treatment during the study will be recorded in the CRF.

15.12 Leg Activity Monitoring

Bilateral ankle sensors will be worn by subjects for 2 week intervals at Screening (Day -14), Baseline (Day -1) and Months 1, 3, 6, and 9. Data will be provided to a centralized reviewer for analysis. Detailed information regarding leg activity monitoring will be provided separately from this protocol.

15.13 Imaging (MRI), Chest X-Ray, CT, and ECG

MRI

Magnetic Resonance Imaging (MRI) of the brain will be obtained using either a 1.5 or 3 Tesla MRI scanner. Each subject should have all scans conducted on the same scanner if possible (excepting those used for stereotactic planning and post-operative assessments, within 2 weeks of the surgery (implant/sham). Standard T1 and T2 sequences and FLAIR will be obtained, and will be recorded in standard digital format for review. Contrast is to be utilized for MRI procedures at Baseline (Visit 2), Day of surgery (Visit 3B), Day 8 (Visit 5), Month 1 (Visit 6), and Month 12 (Visit 10); all other scheduled MRI to be performed without contrast.

Diffusion tensor imaging (DTI) is an MRI technique which characterizes the magnitude, anisotropy and orientation of the diffusion tensor, using the pulsed-gradient, spin echo pulse sequence with a single-shot, echo planar imaging readout. DTI data will be obtained using whole brain coverage, a maximum of 2.5 mm isotropic resolution and at least 30 diffusion encoding directions and may be obtained using either a 1.5 or 3 Tesla MRI scanner. DTI is required for subjects at assessment sites with DTI capability. DTI is optional for sites without access to DTI-compatible scanners. Perfusion imaging, including DSC, is also required for subjects at assessment sites when the MRI has the capacity.

A centralized imaging core laboratory will be used to confirm lesion size for analysis purposes, develop imaging acquisition protocols, and conduct imaging processing and analyses.

Detailed information regarding MRI procedures will be provided separately from this protocol.

Chest X-ray

Standard chest x-ray techniques will be performed according to the schedule described above.

CT Scans

Standard CT techniques will be performed according to the schedule described above. CT is to be conducted without contrast.

Electrocardiograms

All ECGs will be obtained in the supine position, after the subject has been resting supine for at least 10 minutes. ECGs will be 12 lead with a 10 second rhythm strip. ECGs should be obtained prior to drawing blood samples. With the exception of Visit 3 ECG, all attempts should be made to use the same ECG recorder for all visits within individual subjects. ECGs will be centrally read at a core lab according to established quality assurance procedures for inter/intra reader variability. ECGs will be reviewed, signed and dated by the Investigator listed on the Form FDA 1572 (MD or DO) after each ECG collection. The same Investigator should review all ECG reports for a given subject whenever possible.

16.0 ADVERSE EVENTS

16.1 General Information

An **adverse event** (AE) is any untoward medical occurrence in a patient or clinical investigation subject enrolled in the study 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.

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 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 Brochure or product information. Adverse events assessed as related to surgical procedure, and Clavien-Dindo Classification (http://www.surgicalcomplication.info/index-2.html) Grade II or higher would be considered unexpected or unanticipated, unless such event has been previously reported and documented in the IB.

A Serious and Unexpected Suspected Adverse Reaction (SUSAR) is an adverse reaction to study product or surgical procedure that is both serious and unexpected and for which there is a reasonable possibility that the study product or surgical procedure caused the adverse event.

All SUSARs will be submitted as expedited reports to the FDA. For this study, serious and unexpected AEs involving neurological deterioration, procedural complications, seizures, benign and malignant tumors and pregnancy will also be submitted as expedited reports, regardless of attribution.

16.2 Adverse Event Reporting Period

The adverse event reporting period for this trial begins upon informed consent and ends 12 months after the administration of SB623, or at Early Termination.

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.

16.3 Recording of AEs

All AEs, regardless of severity, seriousness, or presumed relationship to Study Product, 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 MedDRA 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 Product

The Investigator must record his/her opinion concerning the relationship of the AE to study therapy on the Adverse Event CRF. Table 4 below provides guidance for assigning relationship to Study Product.

Table 4: Relationship of Adverse Event to the Administration of the Study Product or Surgery

Not related	No temporal relationship to cell treatment/procedure, or the presence of a reasonable causal relationship between another drug, concurrent disease, or circumstance and the adverse event (AE).
Unlikely related	A temporal relationship to cell treatment/procedure, but no reasonable causal relationship between cell treatment/procedure and the AE.
Possibly related	A reasonable causal relationship between the cell treatment/procedure and the AE. Information related to withdrawal of cell treatment/procedure was lacking or unclear.
Probably related	A reasonable causal relationship between the cell treatment/procedure and the AE. The event responded to withdrawal of cell treatment/procedure.
Definitely related	A reasonable causal relationship between the cell treatment/procedure and the AE. The event responded to withdrawal of the cell treatment/procedure.

16.5 Reporting Serious Adverse Events

Any Serious Adverse Event, including death that occurs during this study, whether or not the event is considered to be related to the study product or surgical procedure, must be reported immediately **(within 24 hours after the site becomes aware of the event)** to the Safety Monitor (ProPharma Group/PROSAR).

The contact information for reporting SAEs is as follows:

Safety Monitor: Tim Smith, PharmD, BSN (ProPharma Group/PROSAR)

Email: drugsafety@prosarcorp.com

FAX: 866-681-1063

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

A verbal SAE notification must be followed by a completed Serious Adverse Event Report form signed by the Investigator within 24 hours. The report should be as complete as possible without delaying ProPharma Group/PROSAR notification.

Any SAE follow-up information requested by ProPharma Group/PROSAR should be provided in a timely manner.

Upon receipt of notification of any Serious Adverse Event, ProPharma Group/PROSAR, the Unblinded Medical Monitor and the Sponsor will immediately conduct an evaluation of the event and take action indicated by the results of the evaluation. This may include notification to applicable regulatory authorities/federal agencies, other Investigators, IRBs and/or the suspension or termination of the study. The Sponsor will remain blinded during this process. The Investigator is required to report all IND Safety Reports to the local Ethics Committee (EC) or Institutional Review Board (IRB)/Institutional Biosafety Committee (IBC) in accordance with the EC/IRB bylaws.

All additional follow-up evaluations of the SAE must be reported to ProPharma Group/PROSAR. These data should be sent by email as scanned copy or faxed to the Safety Monitor at 866-681-1063 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.

17.0 EXTERNAL DATA SAFETY MONITORING BOARD

An External Data Safety Monitoring Board (DSMB) will evaluate safety and toxicity and mortality rates, and recommend appropriate actions, according to the DSMB Charter. The DSMB will review ongoing study data within one month of the enrollment of subjects at the 25%, 50%, and 75% of the total population. In addition, two or more serious adverse events potentially attributed to SB623 as assessed by the Investigator will trigger a review by the DSMB before continuing enrollment.

18.0 STATISTICAL METHODS

18.1 Analysis Populations

18.1.1 Efficacy Population

The intent-to-treat (ITT) population will include all randomized patients. All efficacy analyses will utilize this population.

18.1.2 Safety Population

The safety population will include all randomized patients that undergo surgery. All safety analyses will utilize this population.

18.2 Statistical Analysis

The Statistical Analysis Plan (SAP) will provide details on the statistical methods planned for this study, and it will be finalized prior to the clinical study database is locked and the treatment is unblinded.

In general, demographics and baseline characteristics will be presented by treatment group. Continuous variables will be summarized by the following descriptive statistics: sample size, mean, median, standard deviation, minimum, and maximum. Discrete variables will be summarized by frequencies and percentages (contingency tables).

18.2.1 Analysis of Efficacy

All efficacy analyses will be performed on the modified intention to treat (mITT) population, which is defined as all randomized patients who complete the surgery treatment procedure (or sham).

18.2.1.1 Primary Efficacy Analysis

The primary analysis will be a comparison of the proportion of SB623 treated subjects (pooling both SB623 doses) to sham surgical controls that achieve an improvement of at least 10 points on the Fugl-Meyer Motor Scale at 6 months from Baseline. A generalized linear mixed model (GLMM) will be utilized using the mITT population. The GLMM model will have the outcome variable, responder of FMMS (either $\geq$ or <10 points improvement in FMMS at Month 6), and independent variables of treatment (SB623 combined doses vs. sham surgical control), FMMS baseline score and pooled surgical site as fixed effects.

Hypothesis

Let $P_{\text{SB623\_ combined doses}}$ and P_{Placebo} represent the proportions of responders who have an improvement of at least 10 points on the Fugl-Meyer Motor Scale at 6 months from Baseline in SB623 combined doses and placebo, respectively. The primary analysis will test the following hypothesis

H_0: $P_{\text{SB623\_ combined doses}} = P_{\text{Placebo}}$ versus the alternate H_1: $P_{\text{SB623\_ combined doses}} \neq P_{\text{Placebo}}$

18.2.1.2 Secondary Efficacy Analyses

Secondary analyses will evaluate a number of endpoints:

- The proportion of SB623 treated subjects (pooling both SB623 doses) that improve at least 1 point on the Modified Rankin Scale (mRS) will be analyzed at 6 months (from

Baseline) using a similar GLMM model to the primary efficacy analysis. The GLMM model will include treatment (SB623 combined doses vs. sham surgical control), mRS baseline score and pooled surgical site as fixed effects.

- The proportion of SB623 treated subjects (pooling both SB623 doses) that improve at least 6 points on the Action Research Arm Test will be compared to sham-surgery controls at 6 months (from Baseline) using a similar GLMM model to the primary efficacy analysis. The GLMM model will include treatment (SB623 combined doses vs. sham surgical control), ARAT baseline score and pooled surgical site as fixed effects.
- The proportion of SB623 treated subjects (pooling both SB623 doses) that improve at least 1 functional level on Gait Velocity will be compared to sham-surgery controls at 6 months (from Baseline) using a similar GLMM model to the primary efficacy analysis. The GLMM model will include treatment (SB623 combined doses vs. sham surgical control), Gait Velocity baseline score and pooled surgical site as fixed effects.
- The mean change in the two of the four NeuroQOL subdomain T scores of SB623 treated subjects (pooling both SB623 doses) will be compared to sham-surgery controls at 6 months (from Baseline) using a mixed model repeated measures model (MMRM). The two subdomains include:
  - Upper Extremity Function (Fine Motor ADL)
  - Lower Extremity Function (Mobility)

  The MMRM model will include treatment, visit, pooled site, corresponding baseline subdomain T score, and the treatment-by-visit interactions. Restricted Maximum Likelihood Estimation procedure will be employed using an unstructured covariance matrix. Missing observations will not be imputed for this analysis.
- The proportion of SB623 treated subjects (pooling both SB623 doses) scoring either 7 (much better) or 6 (a little better, meaningful) on the Global Rating of Perceived Change by both Subject and Clinician will be compared to sham-surgery controls at 6 months (from Baseline) using a logistic regression model with treatment (SB623 vs. sham placebo) and pooled center as the covariates. The outcome variable of this analysis is a dichotomized variable based on of the Global Rating of Perceived Change score (≥6 vs. <6).
- All efficacy endpoints mentioned above will be analyzed to assess the treatment difference between SB623 2.5-million and 5-million cells groups. The same statistical methodologies to evaluate SB623 combined doses vs. surgical sham control for each efficacy endpoint will be used.

18.2.1.3 Exploratory Efficacy Analyses

The analyses of exploratory efficacy endpoints will be detailed in the SAP.

18.2.1.4 Subgroup Analysis

Inferential analyses will be performed on some subgroups of interest. Details of the subgroup analyses will be included in the SAP.

18.3 Analysis of Safety

All safety analyses will be performed on the safety population.

Adverse events (AEs), discontinuation due to AEs, and serious adverse events (SAEs) will be summarized by presenting, for each treatment group, the number and percentage of patients having any adverse event, having an adverse event in each system organ class and having each individual adverse event. Adverse events will further be categorized for each individual AE by severity, relationship to study drug, and action taken. Other information collected will be listed as appropriate. The summary of AEs will be limited to treatment emergent AEs (TEAEs), which are defined as any adverse event with onset on or after the initiation of treatment or any adverse event already present that worsens in intensity following exposure to study treatment.

Summary statistics for vital signs and laboratory values will be provided. Vital signs and laboratory data will be summarized by presenting shift tables, by presenting summary statistics of raw data and change from baseline values (means, standard deviations, medians, ranges) and by the flagging of abnormal values in data listings.

18.4 Multiplicity Considerations

There are no multiplicity considerations for this study.

18.5 Missing Data

Every effort will be made to reduce the number of dropouts and to document reasons for dropping out.

18.6 Pooling Strategy for Surgical Sites

Some surgical sites may not have sufficient number of subjects for the efficacy analyses. Small surgical sites will be pooled by size within geographic region if necessary. Details of the pooling will be described in the study statistical analysis plan (SAP).

18.7 Determination of Sample Size

The sample size was estimated based on the primary efficacy endpoint, proportion of responders, which is defined as ≥10 points on the FMMS, at Month 6 LOCF (last observation carried forward). Based on the results on the Phase 1/2a study it was assumed that the responder rate was 33% for the SB623 treatment group. Given high surgical placebo response rates (Meissner et al., 2013) it was assumed that the responder rate in the surgical sham was 11.7% (i.e. 35% of the treatment responder rate). Assuming a 80% power, alpha level of 0.05 (two-tailed test), and 2:1 (pooled SB623 treatments: sham control) ratio of randomization, a sample size of 138 (92 subjects in treatment group and 46 subjects in control group) is required to detect this 21.3% difference in the proportion of FMMS responders. Based on a 10% upward adjustment to compensate for dropout patients, a total of approximately 156 subjects (104 treatment and 52 control) will be required.

18.8 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 Product, 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 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.

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 noted in the Protocol Modifications section below. 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.

The results from Screening and data collected during the study (except data that are electronically transferred) will be recorded in the subject’s electronic CRF. The study sites will use an EDC system (Medidata RAVE) that is compliant with relevant FDA regulatory

requirements per 21 CFR Part 11. Password protected access to the EDC system will be via a secure website. Data queries and data corrections will be handled through the same system. All transactions within the EDC system are fully documented within an electronic audit trail. Each set of completed CRFs must be reviewed and electronically signed and dated by the Investigator.

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 Computerized Systems Used for Source Data

A list of the computerized systems that will be used to create, modify, maintain, archive, retrieve, or transmit source data are presented below, pursuant to the Guidance for Industry Computerized Systems Used in Clinical Investigations, May 2007.

Table 5: Computerized Systems Used for Source Data

Protocol Step	Computerized System Type or Description
Informed Consent	A
Demographics	A
Inclusion/Exclusion Review	A
Eligibility Criteria Review	A
Randomization	C
Medical History (including stroke history)	A
Subject Exercise Diary	A
Leg Activity Monitor	D
Urine Pregnancy Test	A
Serum Pregnancy Test	B
Physical Examination	A
Vital Sign Measurements	A
Chest X-ray	A
12-lead ECG	D
Clinical Laboratory Evaluation (Hematology and Serum Chemistry)	B
INR	B
HLA Typing of each Subject	B
ApoE4 & BDNF Val66Met genotyping	B
Occult Malignancy	B
CESD-R Scale	A
Head CT	A
Imaging – Head MRI	D
Imaging – Diffusion Tensor Imaging	D
Modified Rankin Score	A
Motricity Index	A
Fugel-Meyer Motor Score	A
ARAT	A
Gait Velocity	A
NeuroQoL (2 subdomains)	A
Global Rating of Perceived Change (subject and clinician)	A
Adverse Events	A
Serum for anti-HLA Antibodies	B
PBMC Sample	B
Concomitant Medications	A
Sham Surgery or Cell Administration	A
Statistical Analysis	SAS®, version 9.4 or higher

A = EDC (Medidata RAVE); B = LIMS; C = IVRS; D = Core Laboratory Overread.

19.8 Maintaining Records

A study binder must be maintained at the investigative site for study documents, 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 15 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, and study reports.

19.9 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 via access to the secure website. Discrepancies will be resolved with the Investigator as appropriate.

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

- 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.

19.10 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.

19.11 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. Individual investigators will not publish details of specific subjects separately from the results of the entire trial.

20.0 APPENDIX A: JUSTIFICATION FOR STUDY ENDPOINTS

To overcome the perceived limitations of composite scales or global measures of disability, several narrow domain outcome measures have been devised, validated and applied to the assessment of clinical recovery in the chronic stroke setting. These narrow domain outcome measures fall along a continuum of measurement moving from measurements at the level of body function or structure to those focused on participation and life satisfaction.[1] Consistent with the WHO ICF conceptual framework, we propose using narrow domain outcome measures that address the three primary levels of human functioning – the body or body part, the whole person and the whole person in relation to his/her social context.[1] Given that the focus of SB623 is to treat chronic stroke patients with persistent deficits in the *motor* domain of neurological function, the outcome measures we propose to use in our P2b study include:

- Impairment (or Body Function/ Structure): Fugl-Meyer Motor Scale (Primary Endpoint)
- Disability (or Activity):
    - Upper Extremity Motor – Action Research Arm Test (Secondary Endpoint)
    - Lower Extremity Motor – Gait Velocity (Secondary Endpoint)
- Handicap (Participation/ Life Satisfaction): NeuroQOL subdomains (Secondary Endpoints) -
    - Upper Extremity Function
    - Lower Extremity Function

20.1 Justification for use of the Fugl-Meyer Motor Scale as primary endpoint

The F-M scale was developed specifically because prior scales focused on ADLs and measures of global function and not on specific improvements in the neuromuscular function of the affected limb. The need that gave rise to the F-M scale was for a specific and quantitative method for measuring recovery from hemiplegia.[2] The F-M scale is now one of the most widely recognized and clinically relevant measures of body function impairment after stroke.[3] The motor component of the F-M scale in particular has well-established reliability and validity across different stroke recovery time points including chronic stroke.[2, 4]

The F-M scale assesses several dimensions of impairment, including range of motion, pain, sensation, upper extremity, lower extremity, and balance.[5] The specific items in the upper-extremity subsections were derived from the Brunnstrom's stages of post-stroke motor recovery.[6] The items of the F-M are mainly scored on a 3-point Likert-type ordinal scale, from 0 to 2 applied to each item, and the items are summed to provide a maximum score of 226. The motor domain includes items measuring movement, coordination, and reflex action about the shoulder, elbow, forearm, wrist, hand, hip, knee, and ankle. The motor score ranges from 0 (hemiplegia) to a maximum of 100 points (normal motor performance).[2] The F-M motor component consists of the 33-item upper-extremity subscale (UE-FM) and the 17-item lower-extremity subscale (LE-FM).[5] The UE-FM ranges from 0 to 66[7] and the LE-FM from 0-34. The use of these subscales can be used alone to lessen the patient burden of the full questionnaire. For example,

many of the chronic stroke studies described below use the UE-FM alone to evaluate the specific effects of therapeutic intervention on upper limb motor function.

The F-M scale assesses several impairment dimensions and has been extensively used in studies with **chronic** stroke patients. In fact, in a systematic review of RCTs examining robot assisted therapy in chronic stroke, 60% of the RCTs included in analysis used the F-M scale as the primary outcome parameter.[8] More recent RCTs investigating the use of patients continue to use the F-M motor scale as the primary outcome measure.[9-12] Other studies include constraint induced therapy trials[13, 14], brain-machine interface[15], transcutaneous electrical nerve stimulation (primary outcome measure)[16, 17] and mirror therapy (primary outcome measure in this 33 patient RCT).[18]

20.2 Rationale for Narrow Domain Outcome Measures in Chronic Stroke Patients with Motor Deficit

The neurological deficit associated with stroke depends on the location, extent and pattern of resolution of the infarction. Deficits can involve different neurological domains such as: motor, sensory, cognitive, attention, language, visual, coordination and gait. These domain specific deficits can occur alone or in combination. Each of these domains can dominate the clinical presentation of stroke to a greater or lesser extent and may demonstrate different patterns of recovery.[19]

In contrast to acute stroke, the chronic phase of stroke recovery is associated with incremental improvements in neurological function that typically occur asymmetrically in time and extent across these different domains. Often the magnitude of clinical improvement seen in chronic stroke patients is less than in the acute stroke phase and therefore require the use of outcome measures specific to the neurological domain of interest in order to detect clinically meaningful change.

Several narrow domain outcome measures have been devised, validated and applied to the assessment of clinical recovery in the chronic stroke setting. These narrow domain outcome measures fall along a continuum of measurement moving from measurements at the level of body function or structure to those focused on participation and life satisfaction.[1]

Justification for the specific choice of the Action Research Arm Test (ARAT) and Gait Velocity as narrow domain outcome measures that assess changes in the level of *disability* in the upper and lower extremity respectively of chronic stroke patients with motor deficits is provided below.

20.3 Justification for use of the Action Research Arm Test (ARAT) as a secondary endpoint

The ARAT is an observer-rated, performance-based assessment of upper extremity function and dexterity among individuals who sustained cortical damage resulting in hemiplegia.[20, 21] It has been used extensively to measure changes in upper extremity disability following a variety of therapeutic interventions (e.g. mirror therapy, somatosensory stimulation, robot training, transcranial magnetic stimulation and constraint induced therapy) in chronic stroke patients.[22-27] This outcome measure specifically assesses a subject's ability to handle objects differing in size, weight and shape and therefore can be considered to be an arm-specific measure of activity limitation.[28] The ARAT consists of 19 items grouped into four hierarchical subscales: grasp,

grip, pinch, and gross movement.[29] Summation of a 0-3 score in each item yields a total score between 0 and 57.[1]

The ARAT provides a specific assessment of arm function, including proximal control and dexterity and may be predictive of improvement in ADL outcomes.[1] The ARAT appears to be reliable (r = 0.98), valid (rho = 0.92) and responsive with adequate floor and ceiling effects (only 12.5 to 17% of patients scoring the lowest or highest scores) in subjects with stroke .[29]

The magnitude of change in the ARAT that is considered to be clinically meaningful differs according to the time post stroke. According to Lang *et al*. patient expectations in the acute stroke setting are higher than in the chronic phase where patients may have a greater awareness of how smaller changes may be functionally beneficial and may have lower expectations for full recovery.[30] In chronic stroke patients, a change of at least 6 points on the ARAT has been selected as a clinically meaningful threshold.[24, 31, 32] For example, Murphy et al. found that a decrease in movement time by 5 seconds during the drinking task is associated with 6 points improvement in ARAT score.[33] This is consistent with the fact that change scores of 5–10% of the scale range have been found to be clinically meaningful on a number of health related quality of life measures in a variety of patient populations.[30]

20.4 Justification for use of Gait Velocity as a secondary endpoint

Gait is commonly affected by stroke and Gait Velocity is a useful outcome measure of lower extremity function as walking speed predicts the level of disability.[34, 35] as improvements are correlated with better quality of life.[36] Furthermore, Gait Velocity measures are objective and have well defined thresholds. For example, in the context of chronic stroke, a gait velocity that is greater than 0.8 m/s is associated with full community mobility; 0.4 to 0.8 m/s is associated with short walks in the community; and gait velocity less than 0.4 m/s with mobility limited to the home.[36] In the chronic stroke setting, improvements in gait velocity are known to be related to the baseline level of immobility. Given this fact, the LEAPS trial measured the proportion of subjects that moved at least one functional level of walking.[34, 37] A 20% difference between treatment groups was considered to be clinically meaningful.[35] These transitions from one level to another are associated with improvements in home or community ambulation, functional status, and quality of life.[34] The minimal clinically important difference for improvement in gait velocity for subjects with subacute stroke is 0.16 m/s and based on the results of the LEAPS study there was no significant difference in improvement seen at 6 versus 12 months post intervention.[38]

20.5 Justification for use of NeuroQOL as a secondary endpoint

Justification for choosing two specific NeuroQOL Domains as narrow domain outcome measures that assess changes in the level of *Quality of Life, Satisfaction and Participation* secondary to improvements in upper and lower extremity motor function are provided below.

To address existing limitations of Quality of Life (QOL) scales in neurology such as questionable validity, poor interpretability and disease specific applicability, the National Institute of Neurological Disorders and Stroke devised the NeuroQOL. NeuroQOL is a set of self-report measures that assesses the health-related quality of life (HRQOL) of adults and children with neurological disorders that includes stroke.[39] As outlined in the NeuroQOL User Manual, NeuroQOL is comprised of item banks and scales that evaluate symptoms, concerns, and issues that have been validated for stroke and other neurological diseases. The domains

included in NeuroQOL were identified through several sources, including an extensive literature review, an on-line Request for Information (RFI), two phases of in-depth expert interviews (n = 44 and n = 89, respectively), patient and caregiver focus groups (N = 11 groups) and individual interviews with patients and proxies (N = 63). On the basis of this input, 17 Health-Related QOL domains and sub-domains were chosen for adults. Items were selected for inclusion in each domain through a multi-step, iterative process whereby candidate items were reviewed to ensure relevance, translatability, clarity and comprehensive content coverage. The resultant sets of items (item pools) underwent calibration using Item Response Theory (IRT) analyses to form the final item banks and scales. The scales and short forms (8-10 items) from each bank were subsequently validated in adult and pediatric clinical samples.[40] In short, the validity of the NeuroQOL measures for adults with stroke is supported with satisfactory internal consistency, test-retest reliability and significant correlations with many external validity measures.

20.6 Justification for choice of NeuroQOL Domains

Neuro-QOL instruments were developed to be appropriate for a range of neurological conditions. They are not disease-specific measures. Consequently, researchers will need to consider what domains of self-reported health are worth assessing within a given disease and within a given study methodology.[39] Given this study's focus on improvements in motor function the following QOL Domains were chosen:

- The Upper Extremity Domain of NeuroQOL measures one's ability to carry out various activities involving digital, manual and reach-related functions, ranging from fine motor to self-care (activities of daily living).
- The Lower Extremity Domain of NeuroQOL measures one's ability to carry out various activities involving the trunk region and increasing degrees of bodily movement, ambulation, balance or endurance.

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21.0 APPENDIX B: 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 (x10^3/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

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

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Metabolic	Hypocalcaemia (mg/dl)	> 8.4	8.4 - 7.8	7.7 - 7.0	6.9 - 6.1	6
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

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

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
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
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

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

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
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
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

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

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
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
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

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

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
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° C (100.4° F)	urticaria, drug fever 38° C (100.4° 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
Fever of unknown origin	Fever of unknown origin	none	37.1 - 38.0° C 98.7° - 100.4° F	38.1 - 40.0° C 100.5° - 104° F	> 40.0° C > 104.0° F for less than 24 hrs	> 40.0° C (>104° 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				

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

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Additional events	Peripheral oedema	analogous to weight gain				
Additional events	Anorexia	analogous to weight loss				

22.0 APPENDIX C: ANTICOAGULANT GUIDELINES

The use of antiplatelet, anti-coagulant, or non-steroidal anti-inflammatory drugs during the conduct of this study will be 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". In summary the following should apply:

- Prospective patients that are taking Warfarin regularly should stop taking Warfarin 5 days before the surgery visit. These patients should re-start Warfarin after surgery as appropriate.
- INR will need to be repeated prior to surgery to confirm patient is off Warfarin (likely performed at the hospital where the surgery is being performed)
- All other anti-platelet drugs (including NSAIDs) should be stopped 7 days prior to surgery
- Patients at high risk for Venous Thromboembolism (VTE) should be covered with prophylactic Low Molecular Weight Heparin (e.g. Lovenox).
- Anticoagulants (including antiplatelet or non-steroidal anti-inflammatory drugs (NSAIDs) should not be recommenced until Day 8 per the protocol unless the patient is at high risk for VTE in which use of LMWH only on postop Day 2 is acceptable.
- Other than patients at high risk of VTE, 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

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