SANBIO INCORPORATED
CLINICAL PROTOCOL

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

PROTOCOL #:	TBI-01
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Signature Date

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Investigator Name (Printed)

Signature Date

Investigator Statement

I have read the protocol, including all appendices, and I agree it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct the study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practice and International Conference on Harmonization guidelines, and will make a reasonable effort to complete the study within the time designated. 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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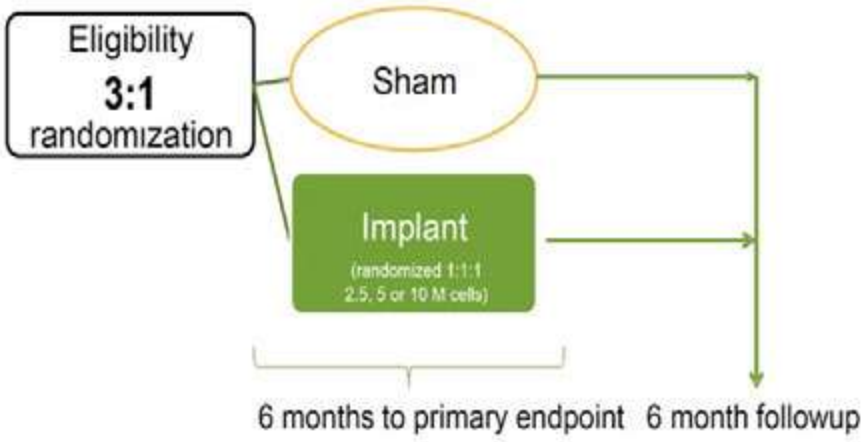
1.0 PROTOCOL SYNOPSIS

Protocol #:	TBI-01
Title:	A Double-Blind, Controlled Phase 2 Study of the Safety and Efficacy of Modified Stem Cells (SB623) in Patients with Chronic Motor Deficit from Traumatic Brain Injury (TBI)
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 cells that have been transiently transfected with a plasmid construct encoding the intracellular domain of human Notch-1. SB623 cells secrete trophic factors that protect neurons in models of ischemic insult. In addition, beneficial matrix protein is also secreted. In a rat contusion model of TBI, implantation of SB623 around the area of the injury resulted in significant improvement of motor function. The safety of implanted SB623 cells has been 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. The 6-month interim study report has 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 likely 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. Given that the cells, dosage and route of administration in this Phase 2 TBI study will be the same as those used in the Phase 1/2a Chronic Stroke study for which no safety concerns with SB623 were seen, we propose

	initiating a double-blind, controlled study design. The primary efficacy endpoint will be the Fugl-Meyer Motor Scale score, with the following as secondary endpoints:
	• Disability Rating Scale score
	• Action Research Arm Test score
	• Gait Velocity
	• NeuroQOL (Upper Extremity Function and Lower Extremity Function)
	• Global Perception of Change:
	  o By Subject (may be completed by Caregiver)
	  o 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 TBI. The study will be conducted at approximately 30 sites in North America (i.e., US), Eastern Europe (i.e., Russia and Ukraine), and Asia Pacific (i.e., Japan). Patients will have moderate or severe TBI with Glasgow Outcome Scale-Extended (GOS-E) scores of 3-6 and stable motor deficits (defined as at least 12 months post-TBI) to be eligible for study participation. Motor deficits are defined as a Motricity Index Upper Extremity score of 10-81, at least two scores less than 33 with one of these less than 25, and at least one score greater than 0 (Upper Extremity [UE] Scale), and/or a Lower Extremity score of 10-78, at least two scores less than 33 with one of these less than 25, and at least one score greater than 0 (Lower Extremity [LE] Scale). Two groups, Group 1 and Group 2, will receive either SB623 or sham surgery in a 3:1 randomization scheme. Group 1 will be further randomized in a 1:1:1 ratio to receive either 2.5, 5 million or 10 million SB623 cells. Randomization will be performed via an interactive web response system (IWRS). For subjects enrolled outside of Japan, the randomization will be stratified by Glasgow Outcome Scale-Extended (GOS-E) score (i.e. scores 3, 4, 5 or 6); for subjects in Japan, the randomization will not be stratified.  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), 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 (Lunsford LD, Niranjan A, Khan AA, Kondziolka D).

	Establishing a Benchmark for Complications Using Frame-Based Stereotactic Surgery. Stereotact 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 at least 1.5 tesla. A safe trajectory is to be defined to enter a cortical gyrus, sparing a sulcus. Implant sites are to be determined in the cortical or cerebral motor sites adjacent to the injured area. Three needle tracks are to be determined with trajectories to surround the damaged area, 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 damaged area. The solid stylet is then to be removed, followed by insertion into the stabilizing cannula of an implantation needle with back-loaded Hamilton syringe (previously qualified for product stability and delivery and provided by the Sponsor, as needed) down to the deepest target point for the first implantation. Five 20-µL volumes of cells are to be injected slowly (approximately 10 µL/min.) into 5 implantation sites, slowly withdrawing the needle to produce equally spaced implants (intervals of 5-6 mm) within the cerebral motor sites adjacent to the injured region. 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 (OR) 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 (Day 2) to ensure 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 surgical treatment. Safety will be monitored by the Investigator, Principal Monitor, Medical Monitor (Unblinded and Blinded), and an external Data Safety Monitoring Board including clinical symptoms, laboratory findings, and head MRI. 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 at 25%, 50%, 75% and 100% enrollment. The DSMB shall be the final arbitrator for attributions. Efficacy will be determined based on changes in the clinical measures of TBI through standardized assessments (Fugl-Meyer Motor Scale (FMMS), Disability Rating Scale (DRS), Action Research Arm Test (ARAT), Gait Velocity, two Domains of the NeuroQOL and the Global Perception of Change (subject and clinician). 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 and post-surgery 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. Note that in this document DSC and Perfusion Imaging are used interchangeably. Primary and secondary efficacy assessments will be completed solely by blinded study personnel (i.e. assessment site efficacy assessor) that do not have access to patient study safety information (this include adverse events, concomitant medications, progress notes, MRI reports, etc.). <u>Stopping Rules</u>: 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 and seizures, shall be subject to review by the DSMB. <u>The DSMB shall be the final arbitrator for attributions.</u>

Patient Population	Adult male or female patients with stable, chronic motor deficits secondary to focal traumatic brain injury. Stable TBI will be defined as at least 12 months post TBI. This requirement is based on a number of studies that have shown that the majority of TBI patients are stable by 6-12 months post-TBI.
Statistical Considerations	For a two-sample t-test to show superiority of SB623 over sham control, assuming 80% power, alpha of 0.05, a two-tailed test, and 3:1 randomization, a sample size of 48 (36 subjects in the treatment group and 12 subjects in the control group) is required. This assumes the mean change from baseline to 6 months in the FM-Motor Scale score is 10.0 for the treatment group (pooling all SB623 doses) and 3.0 for the control group, with an assumed standard deviation of 7.25 in each group. Based on an 8% upward adjustment to compensate for dropout patients, a total of approximately 52 subjects will be required. Since the analysis of efficacy is to be based on the modified ITT population, subjects will continue to be enrolled in the study until there are a total of approximately 52 subjects in the mITT population. The vast majority of subjects will be from outside of Japan; however, a sufficient number of Japanese patients are to be enrolled in order to address Japanese regulatory requirements. For efficacy analyses, comparing treatment to control, all three dose groups will be combined. In addition, a possible SB623 dose-response will be evaluated.
No. of Patients	Approximately 52 subjects
No. of Study Sites	Approximately 30 sites

Inclusion Criteria	1. Age 18-75 years 2. Documented history of TBI, with correlated MRI or CT 3. At least 12 months post-TBI 4. Focal cerebral injury able to be identified on MRI (+/– concomitant diffuse axonal injury) 5. Neurological motor deficit substantially due to focal cerebral injury observed on MRI 6. GOS-E score of 3-6 (i.e. moderate or severe disability) 7. Require Motricity Index UE Scale of 10-81, at least two scores less than 33 with one of these less than 25, and at least one score greater than 0, and/or a LE Scale of 10-78, at least two scores less than 33 with one of these less than 25, and at least one score greater than 0. 8. Able and willing to undergo computed tomography (CT) and magnetic resonance imaging (MRI) 9. Must agree to use of antiplatelet, anticoagulant, or non-steroidal anti-inflammatory drugs to be in accordance with the Anticoagulant Guidelines described in Appendix C. 10. Subjects must be willing to participate in study related exercises 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. Able to undergo all planned neurological assessments 13. Ability of patient to understand and sign an Informed Consent

Exclusion Criteria	1. History or presence of any other major neurological disease 2. Any seizures in the prior 3 months 3. The presence of contracture at any joints that would interfere with interpretation of any of the neurological assessments (*e.g.*, contracture preventing the detection of any increase in the range of motion or ability to perform a task) 4. Other neurologic, neuromuscular or orthopedic disease that limits motor function 5. Clinically significant finding on MRI of brain not related to TBI 6. Known presence of any malignancy except squamous or basal cell carcinoma of the skin 7. History of CNS malignancy 8. Positive findings on tests for occult malignancy, unless a non- malignant etiology is confirmed 9. Uncontrolled systemic illness, including, but not limited to: hypertension (systolic >150 mm Hg or diastolic >95 mm Hg); diabetes; renal, hepatic, or cardiac failure 10. Uncontrolled major psychiatric illness, including depression symptoms (CESD-R Scale of ≥16) 11. Total bilirubin >1.9 mg/dL 12. Serum creatinine >1.5 mg/dL

	13. Hemoglobin <10.0 g/dL 14. Absolute neutrophil count <2000/mm^3 15. Absolute lymphocytes <800/mm^3 16. Platelet count <100,000/mm^3 17. Liver disease documented by AST (SGOT) or ALT (SGPT) ≥2.5 x institutional upper limit of normal 18. Serum calcium >11.5 mg/dL 19. Unexplained abnormal preoperative test values (blood tests, electrocardiogram [ECG], chest X-ray); x-ray evidence of infection; uncontrolled atrial fibrillation or uncontrolled congestive heart failure 20. Presence of craniectomy (without bone flap replacement) or other contraindication to stereotactic surgery 21. Participation in any other investigational trial within 4 weeks of initial screening or within 7 weeks of study entry 22. 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. (interventional treatment refers to treatment done with special equipment which is typically performed in a surgical or procedural type facility - this does not apply to oral medications such as oral baclofen) 23. Ongoing use of herbal or other non-traditional drugs 24. Substance use disorder (per DSM-V criteria, including drug or alcohol) 25. Contraindications to head CT or MRI 26. Pregnant or lactating 27. Female patients of childbearing potential unwilling to use an adequate birth control method during the 12 months of the study 28. 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 29. Patients with allergic reactions to the ingredients of SB623, the drugs used when administering SB623 or the drugs used in testing (applicable for Japan only)

Dosage, Mode of Administration, and Treatment Duration	SB623 cells are provided as a 1-mL sterile cell suspension, containing ≥8 X 10^6 cells/mL, cryopreserved in CryoStor™ freezing media. Cells are provided in individual 2-mL Nalgene™ cryovials with screw caps. Cells to be administered stereotactically only once through one burr-hole craniostomy within and adjacent to the injured area using 3 needle tracks and 5 cell deposits per track at varying depths (20 µL per deposit): • 2.5 X 10^6 SB623 Cells (8.3 X 10^6 cells/mL) • 5.0 X 10^6 SB623 Cells (17 X 10^6 cells/mL) • 10.0 X 10^6 SB623 Cells (33 X 10^6 cells/mL) Details for preparation of the cell suspension for administration and for loading the syringe in the OR will be provided by the Sponsor in a separate document. Clinical sites will be provided necessary materials for reconstitution of the cells and will be trained by the Sponsor. The cryopreserved cells will be thawed, washed, centrifuged, and re-suspended in Plasma-Lyte A at varying concentrations for administration to the patient within approximately 3 hours of dose release. 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 ensure continued sterility. If the endotoxin level is > 5 EU/mL or the gram stain is positive, implantation will not occur. If the sterility test is positive, an investigation will be conducted to determine the source of the contamination by the sponsor. 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. SB623 cells will be kept frozen in vapor phase liquid nitrogen or in storage equipment maintaining the same temperature as vapor phase liquid nitrogen, at study sites, either within the shipping or other acceptable storage container approved by the Sponsor until ready for use. SB623 cells will then be thawed, washed, and re-suspended in Plasma-Lyte A® at the concentration summarized above. Sites will be trained in proper cell handling procedures and these will be documented.
Duration of Patient Study Participation	Twelve months post-randomization (except if there is an unresolved adverse event, in which case the patient will be followed until the adverse event has resolved or a stable clinical endpoint has been reached).

Efficacy Parameters	• Primary Efficacy Endpoint:
	  • Change from baseline in Fugl-Meyer Motor Scale (FMMS) score at Week 24 among all patients
	• Secondary Efficacy Endpoints:
	  • Change from baseline in Disability Rating Scale (DRS) score at Week 24 among all patients
	  • Change from baseline in Action Research Arm Test (ARAT) total score at Week 24 among upper extremity deficit patients
	  • Change from baseline in Gait Velocity at Week 24 among lower extremity deficit patients
	  • Change from baseline in T scores at Week 24 of NeuroQOL Domains:
	  o Upper Extremity Function (Fine motor ADL) among upper extremity deficit patients
	  o Lower Extremity Function (Mobility) among lower extremity deficit patients
	  • Global Rating of Perceived Change scores at Week 24 (from baseline) among all patients: assessed by the subject (may be completed by caregiver) and by the clinician
	For the mITT Population, patients with a Motricity Index UE Scale score at Screening of 10-81 will be considered to have an upper extremity deficit, and patients with a LE Scale score at Screening of 10-78 will be considered to have a lower extremity deficit. For the Per Protocol Population, patients with a Motricity Index UE Scale score at Screening of 10-81, at least two scores less than 33 with one of these less than 25, and at least one score greater than 0, will be considered to have an upper extremity deficit, and patients with a LE Scale score of 10-78, at least two scores less than 33 with one of these less than 25, and at least one score greater than 0, will be considered to have a lower extremity deficit.

Safety Parameters	• All adverse events whether or not related to SB623 or the 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 Endpoints & Analyses	• Change from baseline in Fugl-Meyer Motor Scale (FMMS) score at Week 24 among patients with both upper and lower extremity deficits • Change from baseline in Fugl-Meyer Motor upper-extremity subscale (UE-FM) score at Week 24 among upper extremity deficit patients • Change from baseline in Fugl-Meyer Motor lower-extremity subscale (LE-FM) score at Week 24 among lower extremity deficit patients • Improvement by ≥6 points at Week 24 from Baseline in UE-FM score among upper extremity deficit patients • Improvement by ≥3 points at Week 24 from Baseline in LE-FM score among lower extremity deficit patients • Improvement by ≥10 points at Week 24 from Baseline in Fugl-Meyer Motor Scale (FMMS) score among patients with both upper and lower extremity deficits • Improvement by ≥6 points at Week 24 from Baseline in Action Research Arm Test (ARAT) score among upper extremity deficit patients • Improvement of 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] at Week 24 from Baseline in Gait Velocity on standard 10 m walk among lower extremity deficit patients • Pre- and post-contrast standard T1 and T2 weighted, dual echo, and FLAIR-MRI among all patients • Perfusion MRI among all patients • Diffusion tensor imaging (DTI) with tractography among all patients • Lower limb motion as measured by leg activity monitor among lower extremity patients (applicable for US and Japan only) • Outcome analysis among all patients based on genotyping of polymorphisms at 3 specific loci: HLA; BDNFVal66Met; and ApoE
Interim Analysis	The primary efficacy end point is at 24 weeks. Therefore an interim analysis is planned after all randomized subjects who have not dropped out of the study have completed their 24 weeks visit, to facilitate strategic discussion with regulatory agencies for future plans of the program.

2.0 BACKGROUND

2.1 Medical Need

Traumatic brain injury (TBI) results from a sudden and external physical impact to the head, and often leads to motor (*e.g.*, loss of ambulation, balance, coordination, fine motor skills, strength, and endurance) and cognitive (*e.g.*, loss of communication, information processing, memory, and perceptual skills) impairment. Annually, there are 1.4 million new cases of TBI in the United States alone, resulting in over 50,000 deaths and 80,000 disabilities.[1,2] There are over 5 million Americans (approximately 2% of the population of the United States) currently living with a long-term disability caused by TBI.[2] The economic impact, costing approximately $60 billion (in medical and loss of productivity costs) per year[3], as well as the health and sociological implications prompt the demand for clinically effective treatments.

The physical impact to the brain tissue initially causes necrotic cell death in the underlying tissue, followed by apoptotic cell death in surrounding tissue due to multiple subsequent events such as edema, ischemia, excitotoxicity, increase in free radicals, and altered gene expression.[4,5] Both primary and secondary insults initiate a glial response, which acutely acts to sequester and clean debris at the injury site. Cellular components of the glial scar include reactive astrocytes, which help buffer excess glutamate and secrete neurotrophic factors, and activated microglia, which along with monocyte-derived macrophages, clear out dead tissue. However, extracellular components of the glial scar that forms adjacent to the injury site have been found to inhibit neurite extension (*e.g.*, chondroitin sulphate proteoglycans (CSPGs), Nogo protein), thus limiting regeneration.[6] It has also been appreciated recently that the brain may be attempting to repair through developmental-like processes, as evidenced by the increases in neurogenesis and angiogenesis that occur following TBI.[7,8,9]

2.2 Dual Role of Inflammation in Traumatic Brain Injury

While the brain is considered immune-privileged (due to the tight regulation of the central nervous system microenvironment which largely excludes blood leukocytes from entering), immune responses occur during pathological conditions.[10] In TBI, the initial release of cell contents from the primary necrosis initiates an inflammatory reaction. While inflammation occurring in the brain is associated with deleterious events, the beneficial role of inflammation in TBI has gained appreciation.[11,12,13] The major events of inflammation following TBI are summarized here with an emphasis on the dual nature of this endogenous immune response.

The three major classes of protein mediators of inflammation are cytokines, chemokines, and complement proteins. Pro-inflammatory cytokines (*e.g.*, tumor necrosis factor (TNF), interleukins-1 and -6) are released within minutes following TBI.[13] Studies with specific cytokine knockout mice, as well as in vitro studies indicate that these cytokines may have acute deleterious effects (*e.g.*, blood-brain barrier [BBB] dysfunction, promotion of neuronal death), but are beneficial at later time points (*e.g.*, induce synthesis of anti-inflammatory cytokines, induce neurotrophic factors, promote proliferation of oligodendrocyte precursor cells which may help in remyelination.[13] Neurons and glial cells (astrocytes, microglia, and oligodendrocytes) can produce both chemokines (*e.g.*, TNFα, interferon-γ) and complement proteins (*e.g.*, C3, C5), and have receptors for these proteins. In a similar dual role, chemokines and complement proteins are involved in acute BBB dysfunction and edema, while these proteins eventually lead to increased

nerve growth factor production in astrocytes and microglia. Furthermore, complement proteins have been found to protect neurons from excitotoxicity-induced apoptosis and promote opsonization.[14]

With respect to the cellular aspect of the inflammatory response, microglia (resident brain immune cells) are the first to respond (minutes to hours) by proliferating, and becoming activated microglia which migrate to the area of injury, where they essentially function as macrophages.[15,16] In a traumatic injury, which is associated with increased BBB permeability, leukocytes from the blood can pass through the endothelium at the site of injury; and this process is mediated by cytokines, chemokines, and complement proteins.[14] Neutrophils are the first to infiltrate (hours to days), followed by monocytes (days).[15] Again, there are both beneficial and deleterious roles for these immune cells. The oxidative burst of neutrophils and macrophages is harmful because of the release of oxygen free radicals and neurotoxic enzymes[14], however, both activated microglia and monocyte-derived macrophages aid in clearing debris from dead/damaged cells *via* phagocytosis.[17] Because of the dual nature of the inflammatory response, treatments for TBI that target specific cells or proteins involved in the inflammation response may not be ideal.[4]

2.3 Treatment of TBI

2.3.1 Current Therapies

Current treatment methods in clinical practice primarily aim to reduce intracranial pressure in an effort to minimize brain damage caused by swelling. Examples include moderate hypocapnia and mannitol (first line measures), followed by barbiturates, moderate hypothermia, or a decompressive craniectomy (second line measures) if early attempts fail.[18] However, these therapies have a modest effect on acute brain damage or subsequent cell death pathways, which lead to functional impairment.[19] Furthermore, these treatments do not provide sustained efforts to promote repair or regeneration. Since many TBI patients are young adults, there is a demand for chronic treatments that would prevent further brain damage *and* help repair or compensate for damage that has already occurred. Treatment approaches under investigation for TBI in the past several years aim to target one or more of the pathological events following TBI in an effort to rescue cells or promote repair and regeneration. While many prospective treatments seemed promising in animal models, results in clinical trials have been mixed at best. For example, excitotoxicity results from excess glutamate released from necrotic cells over-stimulating neurons (primarily through NMDA receptors), causing increased intracellular calcium levels and ultimately cell death; and targeting excitotoxicity showed therapeutic potential in animal models. However, various treatments that mediate along this path, such as glutamate antagonists, were not found to be effective for humans with TBI.[20,21] Similar results occurred with other investigational drugs including free radical scavengers and steroids.[22] These treatments may have failed in the clinic because they target pathways that are both deleterious and beneficial, thus the dosage and time of treatment are critical to not interfere with normal homeostasis or reparative mechanisms in the brain. Furthermore, these treatments targeted single mechanisms, which may not be enough in light of the multi-faceted pathology.

2.3.2 Experimental Cellular Therapies

The complex pathology that occurs after TBI requires a multi-faceted treatment paradigm. Cell transplantation is a promising treatment strategy due in part to the ability to target a variety of mechanisms in a sustained manner with just a single therapeutic dose. There are numerous investigations into cell transplantation paradigms for TBI with differing cell types and delivery times / locations with varying responses of donor cell function and effects on host recovery.[23] Cell transplantation has already shown promise in the clinic for treating severe TBI[24], and it is important

to move cell transplantation research towards providing effective clinical therapies.

Stem cells are receiving attention as attractive candidate cells for transplantation, due largely to the proliferative and pluri-/multipotent nature of these cells. The fate of these cells is dictated by both in vitro preparation and the host environment. This is important because multipotent stem cells can adapt to the "needs" of the host tissue.[25] Neural stem cells are multipotent stem cells that have the capacity to differentiate into the major cells in the central nervous system: neurons, astrocytes, and oligodendrocytes, and have many potential applications in central nervous system transplantation. Endogenous neural stem cells persist in the adult brain[26,27] and contribute to neurogenesis that occurs throughout adult mammalian life in the olfactory and hippocampal regions.[7,26] Furthermore, the rate of neuro- and gliogenesis increases following injury.[7,8,9,26] This is thought to be an attempt at self-repair and plasticity, but regeneration in the brain is limited due to mechanisms that are not completely understood, but are attributed to an inhibitory environment. Transplanting exogenous neural stem cells (as well as other cell types) into the injured brain may augment the neuro- and gliogenic environment that the brain inherently attempts to create following injury. Moreover, neural stem cells are an attractive candidate for cell transplantation because they could potentially replace cells lost to injury, and they secrete many neurotrophic factors that could help repair and regenerate injured brain tissue.[28] Transplantation of primary neural stem cells has been shown to improve functional recovery following experimental TBI.[29,30,31]

Adult bone marrow-derived mesenchymal stem cells are another promising stem cell for treatment following TBI. Mesenchymal stem cells from the bone marrow are multipotent stem cells that can differentiate into cells in mesodermal tissues (e.g., bone, cartilage, adipose, muscle).[32] There is also evidence that these cells can trans-differentiate into neural cells (including neurons, astrocytes and neural stem cells) in the proper in vitro[33,34] or in vivo[35,36] environments. Mesenchymal stem cells are also known to produce a variety of trophic factors that may be beneficial to the injured and regenerating brain.[37,38] Transplantation of mesenchymal stem cells has been shown to improve functional recovery following experimental TBI.[39]

2.3.3 Stereotactic Surgery

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%).[40]

2.4 Rationale for Use of SB623 cells in TBI

2.4.1 Summary of SB623 Cells Properties

SB623 cells are human bone marrow-derived cells and are being developed as an allogeneic cell therapy for chronic neurological deficits, such as stroke, TBI and other neurodegenerative conditions. SB623 cells are generated under GMP conditions by the transient transfection of bone marrow stromal cells (MASC) with a plasmid encoding the human Notch-1 intracellular domain.[41] 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, cartilage or adipose cells.

2.4.2 Summary of Notch-1 Gene Properties

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

3.0 Overall Experience with Investigational Product

This section includes a brief summary of preclinical and clinical data available on the Study Agent SB623. More detailed information can be found in the Investigator's 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

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 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. The dose levels used were in a standard dose escalation paradigm: 2.5M, 5.0M, and 10.0M cells administered once into the peri-infarct region of the brain. Four stroke measurement scales were used: NIH Stroke Scale (NIHSS), European Stroke Scale (ESS), Fugl-Meyer Scale (FMS), and the Modified Rankin Scale (mRS). All of these scales, except mRS, showed a statistically-significant average improvement over Baseline at 6 months and other time points (see Figures 1-3 below).

Figure 1 European Stroke Scale (ESS)

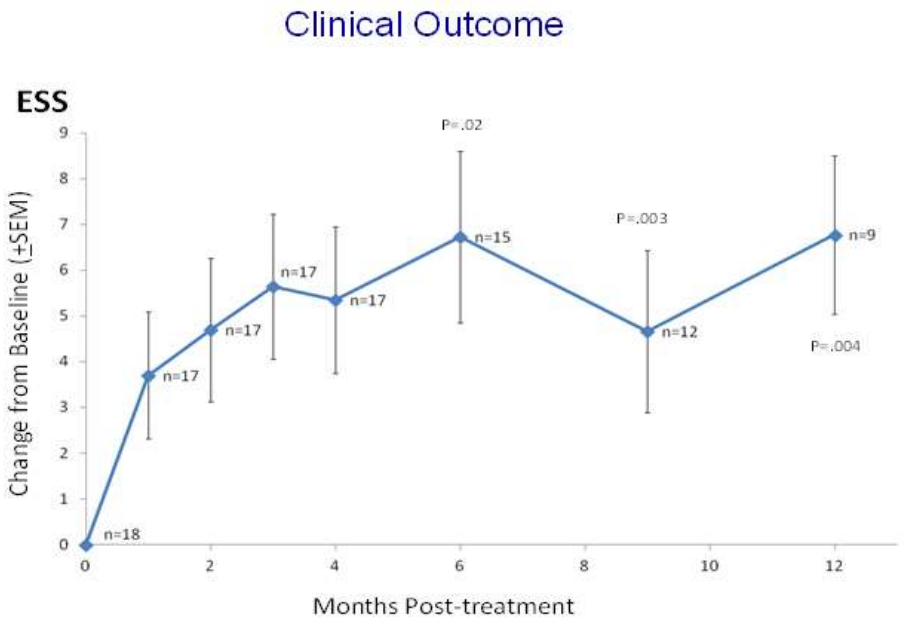


Figure 2 National Institute of Health Stroke Scale (NIHSS)

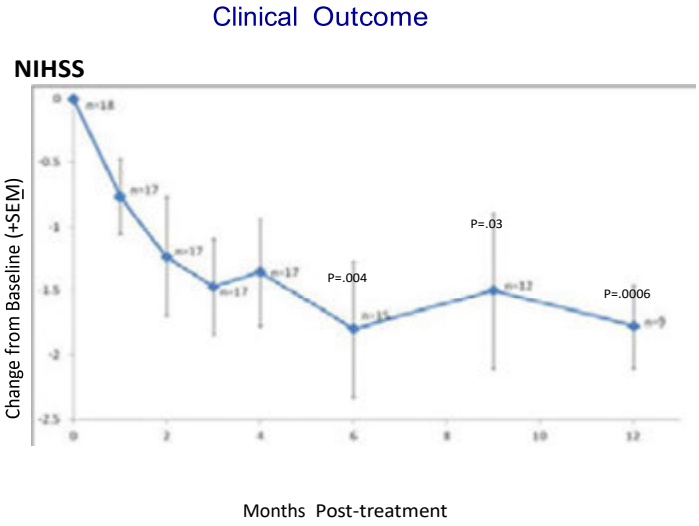
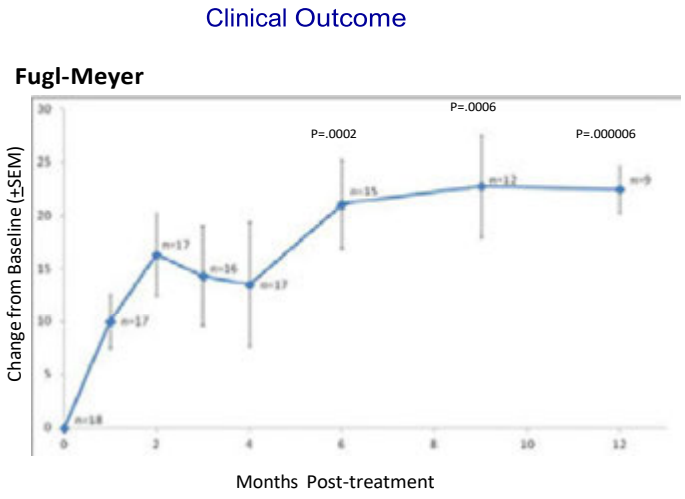


Figure 3 Fugl-Meyer Scale



The FMS scale is considered sensitive to improvements in motor function. Page *et al.* (2012) define a clinically important difference to be a 10% or greater improvement over the scale range.[42] The average improvement score on the FMS in SB-STR01 was 22.19 points, which is a 10% improvement over the 226 point FMS range. Therefore, clinically relevant improvements in impairment scores of patients with chronic motor deficit have been demonstrated by 6 months post intracranial administration of SB623.

3.4 Summary of Known and Potential Risks and Benefits

Based on the available animal data, no risks have been identified, but considerable potential benefit in reversing neurological deficits has been observed in a rat model of TBI and stroke. One 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 likely 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

All dosages of cells are to be administered stereotactically through one burr-hole craniostomy using 3 needle tracks within and adjacent to the focal area of injured brain tissue using 5 cell deposits per track at varying depths, with 20 µL per deposit. Concentrations of cell suspensions to be used will vary depending on the total dosage required per patient. See Table 2 below.

Table 2 Dosages, Volumes and Cell Concentrations

Total SB623 Cells/Pt.	Total SB623 Cells/Deposit	Total SB623 Cells/Track	Concentration of SB623 Cells	Total Volume per Deposit, per Track, and Total
2.5×10^6	1.7×10^5	8.3×10^5	8.3×10^6 cells/mL	20 µL, 100 µL, and 300 µL
5.0×10^6	3.3×10^5	16.5×10^5	17×10^6 cells/mL	20 µL, 100 µL, and 300 µL
10×10^6	6.6×10^5	33×10^5	33×10^6 cells/mL	20 µL, 100 µL, and 300 µL

4.2 Justification

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. The 6-month interim study report has shown statistically-significant improvements in motor function in each of three scales: the ESS, the NIHSS and the FMS. In particular, statistically and clinically significant improvements (i.e. greater than 10% improvement over the scale range) in motor function were noted. The study also showed no serious adverse events likely attributable 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 or antibody responses were observed.

Given that the cells, dosage and route of administration in this Phase 2 TBI study will be the same as those used in the Phase 1/2a study in chronic stroke for which no safety concerns with SB623 were seen, we propose initiating a double-blind, controlled study design. The primary efficacy endpoint will be the Fugl-Meyer Motor Score, with the following scales as secondary endpoints:

- Disability Rating Scale
- Action Research Arm Test
- Gait Velocity
- NeuroQOL (Upper Extremity Function and Lower Extremity Function)
- Global Perception of Change:
    - By Subject (may be completed by Caregiver)
    - By Clinician

Rationales for selecting study endpoints are provided in Appendix A.

The patient population of at least 12 months post-TBI was chosen to allow for stabilization of motor deficits, particularly after physical therapy, and to allow a sufficient number of patients for reasonable accrual.

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 TBI.

5.1 Objectives

5.1.1 Primary Objective

To evaluate the clinical efficacy of intracranial administration of SB623 cells

5.1.2 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.

5.2 Parameters

5.2.1 Efficacy Endpoints

For the mITT Population, patients with a Motricity Index UE Scale score at Screening of 10-81 will be considered to have an upper extremity deficit, and patients with a LE Scale score at Screening of 10-78 will be considered to have a lower extremity deficit. For the Per Protocol Population, patients with a Motricity Index UE Scale score at Screening of 10-81, at least two scores less than 33 with one of these less than 25, and at least one score greater than 0, will be considered to have an upper extremity deficit, and patients with a LE Scale score of 10-78, at least two scores less than 33 with one of these less than 25, and at least one score greater than 0, will be considered to have a lower extremity deficit.

The primary efficacy endpoint is the change from baseline in the Fugl-Meyer Motor Scale (FMMS) score at Week 24 among all patients. The secondary efficacy endpoints are as follows:

- Change from baseline in Disability Rating Scale (DRS) score at Week 24 among all patients
- Change from baseline in Action Research Arm Test (ARAT) total score at Week 24 among upper extremity deficit patients
- Change from baseline in Gait Velocity at Week 24 among lower extremity deficit patients
- Change from baseline in T scores at Week 24 of NeuroQOL Domains:
    - Upper Extremity Function (Fine motor ADL) among upper extremity deficit patients
    - Lower Extremity Function (Mobility) among lower extremity deficit patients
- Global Rating of Perceived Change scores at Week 24 (from baseline) among all patients: assessed by the subject (may be completed by caregiver) and by the clinician

5.2.2 Safety Endpoints

- All adverse events whether or not related to SB623 or the 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

5.2.3 Exploratory Endpoints

- Change from baseline in Fugl-Meyer Motor Scale (FMMS) score at Week 24 among patients with both upper and lower extremity deficits
- Change from baseline in Fugl-Meyer Motor upper-extremity subscale (UE-FM) score at Week 24 among upper extremity deficit patients
- Change from baseline in Fugl-Meyer Motor lower-extremity subscale (LE-FM) score at Week 24 among lower extremity deficit patients
- Improvement by ≥6 points at Week 24 from Baseline in UE-FM score among upper extremity deficit patients
- Improvement by ≥3 points at Week 24 from Baseline in LE-FM score among lower extremity deficit patients
- Improvement by ≥10 points at Week 24 from Baseline in Fugl-Meyer Motor Scale (FMMS) score among patients with both upper and lower extremity deficits
- Improvement by ≥6 points at Week 24 from Baseline in Action Research Arm Test (ARAT) score among upper extremity deficit patients
- Improvement of 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] at Week 24 from Baseline in Gait Velocity on standard 10 m walk among lower extremity deficit patients

Pre- and post-contrast standard T1 and T2 weighted, dual echo, and FLAIR-MRI among all patients

- Diffusion tensor imaging (DTI) with tractography among all patients
- Perfusion MRI among all patients
- Lower limb motion as measured by leg activity monitor among lower extremity deficit Patients (applicable for US and Japan only)
- Outcome analysis among all patients based on genotyping of polymorphisms at 3 specific loci:
    - HLA – degree of donor/recipient mismatch
    - BDNFVal66Met mutation present (yes/no)
    - ApoE (*i.e.*, homo and heterozygosity for ApoE2, ApoE3, ApoE4 alleles)

6.0 SURGICAL AND IMPLANTATION PROCEDURES

The surgical procedure is a modification of one used earlier with another cell product,[43] 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.[40] The procedure is also identical to that being used in the ongoing clinical study in chronic stroke patients. There are to be two groups randomized in a 3:1 ratio: Group 1 (treatment with SB623) and Group 2 (sham surgery control). Group 1 will be further randomized in a 1:1:1 ratio of subjects receiving 2.5, 5 or 10 million cells. On the morning of surgery, a standard stereotactic coordinate frame is to be applied to the head under local anesthesia and mild sedation. Either a head CT scan overlaid on the Baseline MRI or a head MRI scan alone is to be performed for stereotactic targeting. A safe trajectory is to be defined to enter a cortical gyrus, sparing a sulcus. Implant sites are to be determined in the cortical or cerebral motor sites adjacent to the injured area. Three needle tracks are to be determined with trajectories to surround the damaged area, 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 damaged area. The solid stylet is then to be removed, followed by insertion into the stabilizing cannula of an implantation needle with back-loaded Hamilton syringe (previously qualified for product stability and delivery and provided by the Sponsor, as needed) down to the deepest target point for the first implantation. Five 20-µL volumes of cells are to be injected slowly (approximately 10 µL/min.) into 5 implantation sites, slowly withdrawing the needle to produce equally spaced implants (intervals of 5-6 mm) within the cerebral motor sites adjacent to the injured region. 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 (OR) 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 or local standard medical practice require a longer stay. An MRI is to be done on the first post-operative day (Day 2) to ensure there are no significant bleeding risks.

7.0 PATIENT SELECTION

7.1 Inclusion Criteria

1. Age 18-75 years
2. Documented history of TBI, with correlated MRI or CT
3. At least 12 months post-TBI
4. Focal cerebral injury able to be identified on MRI (+/- concomitant diffuse axonal injury)
5. Neurological motor deficit substantially due to focal cerebral injury observed on MRI
6. GOS-E score of 3-6 (i.e. moderate or severe disability)
7. Require Motricity Index UE Scale of 10-81, at least two scores less than 33 with one of these less than 25, and at least one score greater than 0, and/or a LE Scale of 10-78, at least two scores less than 33 with one of these less than 25, and at least one score greater than 0.
8. Able and willing to undergo computed tomography (CT) and magnetic resonance imaging (MRI)
9. Must agree to use of antiplatelet, anticoagulant, or non-steroidal anti-inflammatory drugs to be in accordance with the Anticoagulant Guidelines described in Appendix C.
10. Subjects must be willing to participate in study related exercises 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. Able to undergo all planned neurological assessments
13. Ability of patient to understand and sign an Informed Consent

7.2 Exclusion Criteria

1. History or presence of any other major neurological disease
2. Any seizures in the prior 3 months
3. The presence of contracture at any joints that would interfere with interpretation of any of the neurological assessments (*e.g.*, contracture preventing the detection of any increase in the range of motion or ability to perform a task)
4. Other neurologic, neuromuscular or orthopedic disease that limits motor function
5. Clinically significant finding on MRI of brain not related to TBI
6. Known presence of any malignancy except squamous or basal cell carcinoma of the skin
7. History of CNS malignancy
8. Positive findings on tests for occult malignancy, unless a non-malignant etiology is confirmed

9. Uncontrolled systemic illness, including, but not limited to: hypertension (systolic >150 mm Hg or diastolic >95 mm Hg); diabetes; renal, hepatic, or cardiac failure
10. Uncontrolled major psychiatric illness, including depression symptoms (CESD-R Scale of ≥16)
11. Total bilirubin >1.9 mg/dL
12. Serum creatinine >1.5 mg/dL
13. Hemoglobin <10.0 g/dL
14. Absolute neutrophil count <2000/mm^3
15. Absolute lymphocytes <800/mm^3
16. Platelet count <100,000/mm^3
17. Liver disease documented by AST (SGOT) or ALT (SGPT) ≥2.5 x institutional upper limit of normal
18. Serum calcium >11.5 mg/dl
19. Unexplained abnormal preoperative test values (blood tests, electrocardiogram [ECG], chest X-ray); x-ray evidence of infection; uncontrolled atrial fibrillation or uncontrolled congestive heart failure
20. Presence of craniectomy (without bone flap replacement) or other contraindication to stereotactic surgery
21. Participation in any other investigational trial within 4 weeks of initial screening or within 7 weeks of study entry
22. 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. (interventional treatment refers to treatment done with special equipment which is typically performed in a surgical or procedural type facility - this does not apply to oral medications such as oral baclofen).
23. Ongoing use of herbal or other non-traditional drugs
24. Substance use disorder (per DSM-V criteria, including drug or alcohol)
25. Contraindications to head CT or MRI
26. Pregnant or lactating
27. Female patients of childbearing potential unwilling to use an adequate birth control method during the 12 months of the study
28. 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
29. Patients with allergic reactions to the ingredients of SB623, the drugs used when administering SB623 or the drugs used in testing (applicable to Japan only)

8.0 INVESTIGATIONAL PLAN

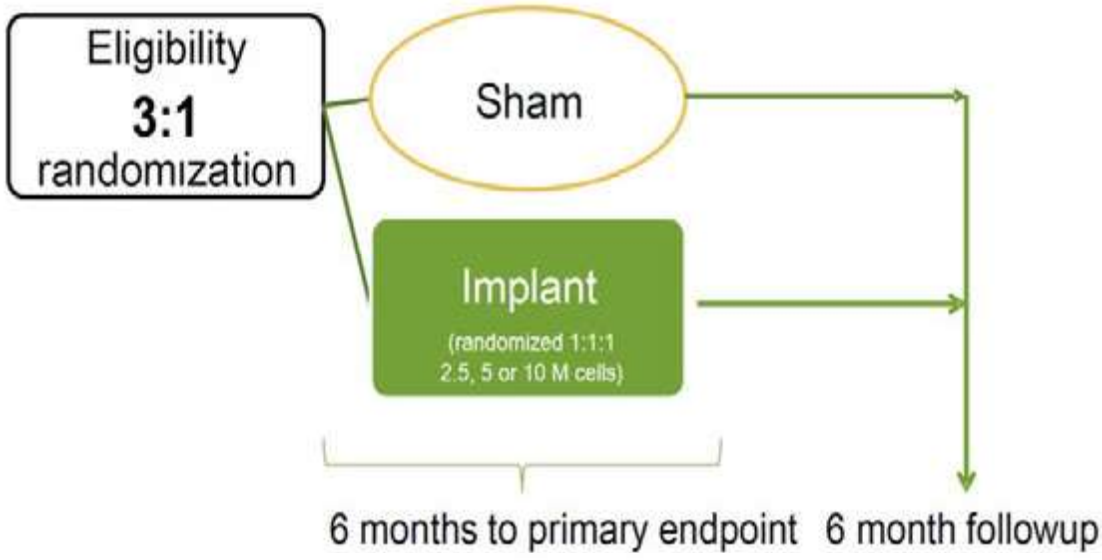
8.1 Overall Study Design

This is a double-blind, sham-surgery controlled study of stereotactic, intracranial injection of SB623 cells in patients with fixed motor deficits from TBI. The study will be conducted at approximately 30 sites in North America (i.e., US), Eastern Europe (i.e., Russia and Ukraine), and Asia Pacific (i.e., Japan).

Two groups, Group 1 and Group 2, will receive SB623 and sham surgery, respectively, in a 3:1 randomization scheme. Group 1 will be further randomized in a 1:1:1 ratio to receive either 2.5, 5 million or 10 million SB623 cells. Randomization will be performed via an interactive web response system (IWRS). For subjects enrolled outside of Japan, the randomization will be stratified by GOS-E score (i.e. scores 3, 4, 5 or 6); for subjects in Japan, the randomization will not be stratified.

The study schematic is shown in the figure below.

Figure 4 Study Schematic



The neurological assessment team evaluating Fugl-Meyer Motor Score 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 by the Investigator, Principal Monitor, Medical Monitor (Unblinded and Blinded), and an external Data Safety Monitoring Board including clinical symptoms, laboratory findings, and head MRI. 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 at 25%, 50%, 75% and 100% enrollment. The DSMB shall be the final arbitrator for attributions. Efficacy will be determined based on changes in the clinical measures of TBI through standardized assessments (Fugl-Meyer Motor Scale (FMMS), Disability Rating Scale (DRS), Action Research Arm Test (ARAT), Gait Velocity, two Domains of the NeuroQOL and the Global Perception of Change (subject and clinician). MRI of the brain

will be performed at scheduled time points and imaging (pre- and post-contrast T1-weighted, dual echo, and FLAIR sequences). MRIs will be analyzed by a central reader and post-surgery 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. Note that in this document DSC and Perfusion Imaging are used interchangeably. Primary and secondary efficacy assessments will be completed solely by blinded study personnel (i.e. assessment site efficacy assessor) that do not have access to patient study safety information (this includes adverse events, concomitant medications, progress notes, MRI reports, etc.).

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 and 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 Study Procedures Flow Chart

Study Period	Screening	Baseline[1]	Sham or Cell	Follow-Up Period				
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study Day	**-84 to -15**	**-14 to -1**	**1**	**2[2]**	**8 (± 1)**	**28 (± 7)**	**84 (± 7)**	**168 (± 7)**
Study Week					**1**	**4**	**12**	**24**
Study Month						**1**	**3**	**6**
Informed Consent	X							
Demographics	X							
Inclusion/Exclusion	X							
Eligibility Criteria Review[3]		X	X					
Randomization			X					
Medical History	X							
Physical Therapy Instruction and Subject Exercise Diary given to subject	X				X	X	X	
Subject Exercise Diary Review		X				X	X	X
Leg Activity Monitor given to subject[1]	X	X						
Leg Activity Monitor data download[4]		X			X	X	X	X
Pregnancy Test[5,6]	X	X						X
Physical Exam	X	X						X
Vital Signs[2]	X	X			X	X	X	X
Chest X-Ray and ECG	X							X
Hematology	X	X			X	X	X	X
Serum Chemistry	X	X			X	X	X	X
INR and APTT		X	X[7]					X
HLA typing of each subject		X						
ApoE4 & BDNF Val66Met genotyping		X						
Occult Malignancy	X							
CESD-R Scale	X							
Head CT			X[8]					

[1] All inclusion and exclusion criteria must be verified to confirm that the patient qualifies for the study prior to proceeding to Visit 3. NOTE: Hematology, Serum Chemistry, APTT and INR at Baseline (Day -14 to -1) 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.

[2] Subjects can stay at hospital until Visit 5 (Day 8) for post-surgery observation due to standard local medical practice.

[3] Screening eligibility is confirmed at the blinded site, and the surgical safety (i.e. ability to proceed safely with surgery) is confirmed at the unblinded site.

[4] Leg Activity Monitors may be replaced at any Visit if the battery is low. If leg activity monitor is dispensed at baseline visit (can be dispensed at screening or baseline), data download will be done at Follow-Up Visit 5.

[5] Only for women of childbearing potential.

[6] Serum β-HCG at Screening (Visit 1), Visit 8, and Visit 10; either serum or urine β-HCG at Baseline (Visit 2).

[7] Both International Normalized Ratio of Prothrombin Time (INR) and Activated Partial Thromboplastin Time (APTT) shall be performed in the local lab prior to surgery; both results must be normal according to local lab (e.g. INR >1.2 and APTT >38 seconds).

[8] Head CT on Day 1 is post-operative.

[1] Mandatory for subjects in US and Japan only
[2] Height and weight should be collected

Study Period	Screening	Baseline[1]	Sham or Cell Admin	Follow-Up Period				
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study Day	**-84 to -15**	**-14 to -1**	**1**	**2**	**8 (± 1)**	**28 (± 7)**	**84 (± 7)**	**168 (± 7)**
Study Week					**1**	**4**	**12**	**24**
Study Month						**1**	**3**	**6**
Imaging--Head MRI[9]	X[11]	X[11]	X[10]	X	X[11]	X[11]		X
Imaging – Diffusion Tensor & Dynamic Susceptibility Contrast Imaging[12]		X				X		X
Clinical TBI Evaluations	X[13]	X[14]				X[14]	X[14]	X[14]
Global Rating of Perceived Change (subject and clinician)						X[15]	X[15]	X[15]
Serum for anti-HLA Antibodies		X			X	X	X	X
PBMC Sample[16]		X			X	X	X	X
Adverse Events		X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
Sham Surgery or Cell Administration[17]			X					

[9] 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)). T1 and dual echo and FLAIR MRI will be obtained, and will be recorded in standard digital format for review.

[10] Or CT overlaid with MRI from Baseline.

[11] MRI with Gadolinium.

[12] 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. Whole brain DTI data will be obtained with at least 30 diffusion encoding directions and may be obtained using either a 1.5 or 3 Tesla MRI scanner. Dynamic Susceptibility Contrast (DSC) Imaging is acquired using single shot gradient echo planar image covering the whole brain. This allows calculation of perfusion parameters.

[13] GOS-E; Motricity Index

[14] Fugl-Meyer Motor Score; Disability Rating Scale, Action Research Arm Test, Gait Velocity, and NeuroQOL (2 Domains). Primary and secondary efficacy assessments will be completed solely by blinded study personnel (i.e. assessment site efficacy assessor) that do not have access to patient study safety information (this includes adverse events, concomitant medications, progress notes, MRI reports, etc.).

[15] Clinician ideally includes assessment site efficacy assessor who does not have access to patient study safety information because Global Rating of Perceive Change is a component of secondary endpoint, thereby maintaining the blind of the trial.

[16] At each time point that serum antibody samples are collected, an additional sample for PBMC will also be collected and stored at the central laboratory

[17] Subjects can be admitted to the clinical site on Day -1 and undergo study surgical procedure on Day 1 only after all other procedures for this visit have been completed. Subjects will be discharged on Day 2 unless complications or local standard medical practice require a longer stay.

Schedule of Assessments (Continued)

Study Period	**Follow-Up Period**	
Study Visit	**9**	**10**[18]
Study Day	**252 (± 14)**	**336 (± 14)**
Study Week	**36**	**48**
Study Month	**9**	**12**
Informed Consent		
Demographics		
Inclusion/Exclusion		
Eligibility Criteria Review		
Randomization		
Medical History		
Physical Therapy Instruction and Subject Exercise Diary given to subject		
Subject Exercise Diary Review		
Leg Activity Monitor data download[4]	X	X
Pregnancy Test[5,6]		X
Physical Exam.		X
Vital Signs	X	X
Chest X-Ray and ECG		X
Hematology	X	X
Serum Chemistry	X	X
INR and APTT		X
HLA typing of each subject		
ApoE4 & BDNF Val66Met genotyping		
Occult Malignancy		
CESD-R Scale		
Head CT		
Imaging--Head MRI[9]		X[11]
Imaging – Diffusion Tensor & Dynamic Susceptibility Contrast Imaging[12]		X
Clinical TBI Evaluations	X[14]	X[14]
Global Rating of Perceived Change (subject and clinician)	X[15]	X[15]
Serum for anti-HLA Antibodies		X
PBMC Sample[16]		X
Adverse Events	X	X
Concomitant Medications	X	X
Sham Surgery or Cell Administration[17]		

[18] Patients who have withdrawn from the study must return for Visit 10 assessments.

9.2 Pre-study Screening 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 -15)

- Inclusion/Exclusion Criteria
- Demographics
- Medical History
- 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 (applicable for US and Japan only)
- Physical Exam
- Vital Signs Including Weight and Height
- Chest X-Ray and ECG
- Hematology
- Serum Chemistry
- Determination of occult malignancy by occult blood in stools (hemoccult test), finding on chest x-ray, carcinoembryonic antigen, prostate-specific antigen (males only), cancer antigen 125 (females only), α-fetoprotein, and β-hCG
- CESD-R Scale Administration (subject must have score of <16)
- Imaging (head MRI) if no head MRI available that was performed within the last 3 months
- Clinical TBI Evaluation (GOS-E and Motricity Index)

9.3 Baseline and Confirmation of Eligibility

9.3.1 Visit 2: Baseline (Day -14 to -1)

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
- Leg Activity Monitor data download (applicable for US and Japan only)

- Vital Signs
- Hematology
- Serum Chemistry
- INR and APTT
- 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) with Gadolinium
- Exploratory Imaging (pre- and post-contrast T1-weighted, dual echo, FLAIR MRI, Diffusion tensor imaging (DTI) with tractography and Dynamic Susceptibility Contrast (DSC) MRI for perfusion imaging)
- Clinical TBI Evaluations (FMMS; DRS; ARAT; Gait Velocity; NeuroQOL (Upper Extremity Function and Lower Extremity Function)

9.3.2 Eligibility Confirmation/Randomization

Confirmation of eligibility can only occur after performing all assessments and verifying that the patient meets the inclusion and exclusion criteria for the study. Screening eligibility is confirmed at the blinded site, and the surgical safety (i.e. ability to proceed safely with surgery) will be confirmed at the unblinded site prior to surgery.

9.4 Cell Administration or Sham Surgery (Visit 3: Day 1)

Subjects can be admitted to the clinical site on Day -1 and undergo study surgical procedure on Day 1. Prior to any procedures, the patient will be queried on the use of any or changes in medication or adverse events that have occurred since Baseline.

The patient will be randomized prior to surgery via IWRS. The surgical staff, especially the surgeon, should make every effort to remain blinded to the assigned treatment until the start of the surgical procedures. The patient's group allocation will be known by the unblinded laboratory staff so that the appropriate SB623 dose can be prepared for the patient (if randomized to Group 1).

Prior to cell implantation, either a head CT overlaid with the Baseline head MRI or a head MRI alone will be done to determine the exact locations for the implants. Both International Normalized Ratio of Prothrombin Time (INR) and Activated Partial Thromboplastin Time (APTT) shall be performed in the local lab prior to surgery, both results must be normal according to local lab (e.g. INR >1.2 and APTT >38 seconds).

Group 1:

One burr hole will be made in the skull of the patient in a location that will allow ready access adjacent to the focal area of injured brain tissue 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

9.5 Visit 4: Follow-Up Period (Study Day 2)

The following will be performed:

- Adverse Events
- Concomitant Medications
- Head MRI
- Subjects will be discharged on Day 2 unless complications or local standard medical practice require a longer stay

9.6 Visit 5: Follow-Up Period (Week 1, Study Day 8 ± 1)

The following will be performed:

- Vital Signs
- Hematology
- Serum Chemistry
- Physical Therapy Instruction and Subject Exercise Diary given to Subject
  - Leg Activity Monitor data download (applicable for US and Japan only)
- Blood draw for Serum anti-HLA Antibodies
- Blood draw for PBMC
- Head MRI with Gadolinium (MRI must be read before re-starting any antiplatelet, anticoagulant, or non- steroidal anti-inflammatory agents)
- Adverse Events
- Concomitant Medications

9.7 Visit 6: Follow-Up Period (Week 4, Study Day 28 ± 7)

- 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
- Leg Activity Monitor data download (applicable for US and Japan only)
- Imaging (head MRI) with Gadolinium
- Exploratory Imaging (Pre- and post-contrast T1 weighted, dual echo, FLAIR MRI, Diffusion tensor imaging (DTI) with tractography and Dynamic Susceptibility Contrast (DSC) MRI for perfusion imaging)
- Clinical TBI Evaluations (FMMS; DRS; ARAT; Gait Velocity; NeuroQOL (Upper Extremity Function and Lower Extremity Function)
- Global Rating of Perceived Change: subject and clinician, 7-point Likert scale
- Adverse Events
- Concomitant Medications

9.8 Visit 7: Follow-Up Period (Week 12, Study Day 84 ± 7)

- 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
- Leg Activity Monitor data download (applicable for US and Japan only)
- Clinical TBI Evaluations (FMMS; DRS; ARAT; Gait Velocity; NeuroQOL (Upper Extremity Function and Lower Extremity Function)
- Global Rating of Perceived Change: subject and clinician, 7-point Likert scale
- Adverse Events
- Concomitant Medications

9.9 Visit 8: Follow-Up Period (Week 24, Study Day 168 ± 7)

- Pregnancy test (serum β-hCG) for women of childbearing potential only
- Physical Exam.
- Subject Exercise Diary Review
- Leg Activity Monitor data download (applicable for US and Japan only)
- Vital Signs
- Chest X-ray and ECG
- Hematology
- Serum Chemistry
- INR and APTT
- Blood draw for Serum anti-HLA Antibodies
- Blood draw for PBMC
- Imaging (head MRI)
- Exploratory Imaging (Pre- and post-contrast T1-weighted, dual echo, FLAIR MRI, and Diffusion tensor imaging (DTI) with tractography and Dynamic Susceptibility Contrast (DSC) for perfusion imaging)
- Clinical TBI Evaluations (FMMS; DRS; ARAT; Gait Velocity; NeuroQOL (Upper Extremity Function and Lower Extremity Function)
- Global Rating of Perceived Change: subject and clinician, 7-point Likert scale
- Adverse Events
- Concomitant Medications

9.10 Visit 9: Follow-Up Period (Week 36, Study Day 252 ± 14)

- Vital Signs
- Hematology
- Serum Chemistry
- Leg Activity Monitor data download (applicable for US and Japan only)
- Clinical TBI Evaluations (FMMS; DRS; ARAT; Gait Velocity; NeuroQOL (Upper Extremity Function and Lower Extremity Function)
- Global Rating of Perceived Change: subject and clinician, 7-point Likert scale
- Adverse Events
- Concomitant Medications

9.11 Visit 10: Follow-Up Period (Week 48, Study Day 336 ± 14) and scheduled early withdraw

- Pregnancy test (serum β-hCG) for women of childbearing potential only
- Physical Exam
- Vital Signs
- Chest X-ray and ECG
- Hematology
- Serum Chemistry
- INR and APTT
- Blood draw for Serum anti-HLA Antibodies
- Blood draw for PBMC
- Imaging (head MRI) with Gadolinium
- Exploratory Imaging (Pre- and post-contrast T1-weighted, dual echo, FLAIR MRI, Diffusion tensor imaging (DTI) with tractography and Dynamic Susceptibility Contrast (DSC) for perfusion imaging)
- Leg Activity Monitor data download (applicable for US and Japan only)
- Clinical TBI Evaluations (FMMS; DRS; ARAT; Gait Velocity; NeuroQOL (Upper Extremity Function and Lower Extremity Function)
- Global Rating of Perceived Change: subject and clinician, 7-point Likert scale
- Adverse Events
- Concomitant Medications

10.0 DESCRIPTION OF STUDY TREATMENT

10.1 Study Product Description

SB623 cells are provided as a 1-mL sterile cell suspension, containing ≥8 X 10^6 cells/mL, cryopreserved in CryoStor™ freezing media.

10.2 Study Product Packaging

Individual 2-mL Nalgene™ cryovial with screw cap

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 within the shipping container provided by the Sponsor, or in storage equipment maintaining the same temperature as vapor phase liquid nitrogen until transferred at the site to a GMP-compliant liquid nitrogen container or other acceptable storage container approved by the Sponsor.

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

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

10.5 Study Product Accountability Procedures

The Investigator will be responsible for maintaining inventory and accounting for all Study Product received from the Sponsor. 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. Any partially used vials are to be destroyed at the site per institutional standard operating procedure. Unopened vials will be stored in the vapor phase of liquid nitrogen, or in storage equipment maintaining the same temperature as vapor phase liquid nitrogen, or other acceptable storage container approved by the Sponsor until returned to the Sponsor.

11.0 TREATMENT ASSIGNMENT AND BLINDING

This is a double-blind study. The blind will be maintained by strict 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 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 the assessment site investigator's discretion. These unblinding events (e.g., local head imaging reading) will be recorded and reported to the Sponsor.
    c. To further safeguard maintenance of the blind, primary and secondary 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, medical charts, etc.,).

d. All sites will be required to document how they will maintain the blind through a Maintenance of the Blind Plan that will require approval and sign off by the Sponsor.

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 IWRS. Date and reason for unblinding are to be recorded and reported to the Sponsor immediately.

12.0 CONCOMITANT MEDICATIONS

All concomitant medications including prescription and over-the-counter drugs taken during the 14 days prior to initial screening or used anytime during the study through 1 year post Study Products will be documented. Documentation through Week 48 will include changes from the prior visit, start and stop dates, dose, and reasons for the medication use.

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

13.0 TERMINATION, DISCONTINUATION & LOST TO FOLLOW UP

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 site and remove all study materials from the study site.

13.3 Patient Discontinuation

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

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

If patient withdrawal occurs during the study period, the Last Evaluation (Visit 10) visit should be performed, if possible, at the time of patient withdrawal or as soon as possible thereafter.

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 may check public records for survival status at 12 months.

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 and seizures, shall be subject to review by the DSMB.

The DSMB shall be the final arbitrator for attributions.

15.0 CLINICAL AND LABORATORY EVALUATIONS AND PROCEDURES

15.1 Medical History

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

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 temperature, blood pressure at rest (while subject is in seated position), heart rate, and respiratory rate. Height and weight will be recorded at Visit 1: Screening only.

15.3 Safety Laboratory

All safety laboratory evaluations will be conducted at a central laboratory. At every sampling time point, approximately 15 mL of blood will be drawn for each of the hematology and serum chemistry panels.

The following laboratory evaluations will be performed:

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

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

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 (i.e., 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.

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. Assays will be done periodically on pooled samples. A central laboratory will be utilized for sample storage and assay.

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.

15.8 Clinical TBI Evaluations

15.8.1 Screening

15.8.1.1 Glasgow Outcome Scale-Extended (GOS-E)

Subjects will require a GOS-E score of 3-6 (i.e. moderate or severe disability) at screening. Specific information on scoring using the GOS-E can be found in the publication.[44]

15.8.1.2 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 both Motricity Index UE score of 10-81 (at least two scores less than 33 with one of these less than 25, and at least one score greater than 0), and/or a LE score of 10-78 (at least two scores less than 33 with one of these less than 25, and at least one score greater than 0).

15.8.2 Study Endpoints

15.8.2.1 Fugl-Meyer Motor Scale (FMMS) Score

The FMMS score will be calculated at Baseline and Weeks 4, 12, 24 (primary), 36 and 48. The treatment group will be compared to the control group based on the mean change from baseline at each month.

15.8.2.2 Disability Rating Scale (DRS) Score

The DRS total will be calculated at Baseline and Weeks 4, 12, 24 (secondary), 36 and 48. The treatment group will be compared to the control group based on the mean change from baseline at each month. Specific information on scoring using the DRS can be found in the publication.[45]

15.8.2.3 Action Research Arm Test (ARAT) Total Score

ARAT scores will be calculated at Baseline and Weeks 4, 12, 24 (secondary), 36 and 48. The treatment group will be compared to the control group based on the mean change from baseline at each month.

15.8.2.4 Gait Velocity

Gait Velocity on a standard 10 m walk will be calculated at Baseline and Weeks 4, 12, 24 (secondary), 36 and 48. The treatment group will be compared to the control group based on the mean change from baseline at each month.

15.8.2.5 NeuroQOL

Two Domains of the NeuroQOL will be assessed at Baseline and Weeks 4, 12, 24 (secondary), 36 and 48 using the Short Forms. The 2 subdomains are the 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 from baseline in T Scores at each month.

15.8.2.6 Global Rating of Perceived Change from Baseline

This assessment will be performed at Weeks 4, 12, 24 (secondary), 36 and 48. It will be performed by both the subject (may be completed by caregiver) and a blinded efficacy assessment clinician (ideally the "assessment site efficacy assessor") who does not have access to patient study safety information, thereby maintaining the blind of the trial. Subjects and clinicians will be asked about perceived changes in the subject's motor function by comparing "how well they are doing compared to before the surgical procedure". 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

15.9 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 and to indicate their performance in a patient diary during Screening and Weeks 4, 12, and 26. The patient's diary will be reviewed at the clinical site to ensure completeness.

15.10 Leg Activity Monitoring

Leg Activity Monitoring is mandatory in the US and Japan only. Bilateral ankle sensors will be worn by subjects throughout the study. The leg activity monitors will be dispensed at either the Screening or Baseline visit, and at least 2 weeks of baseline data will be required. Activity data will be downloaded at the clinical site and changes from Baseline in activity parameters will be calculated at Months 1, 3, 6, 9 and 12.

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

15.11.1 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)). All MRI scans will include T1-weighted, dual echo, and FLAIR MRI. These images will be recorded in standard digital format (DICOM) for review.

On visits 2, 5, 6, and 10 post-contrast MRI will also be acquired. The post-contrast images will be acquired 5 minutes after the administration of the contrast agent. During this waiting period, Dynamic Susceptibility contrast MRI will be acquired for measuring tissue perfusion imaging. This

additional acquisition does not increase the scan time.

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 (EPI) readout. DTI data will be obtained from the whole brain, at least 30 diffusion encoding directions and may be obtained using either a 1.5 or 3 Tesla MRI scanner.

15.11.2 Chest X-ray

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

15.11.3 CT Scans

Standard CT techniques will be performed according to the schedule described above.

15.11.4 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. 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.

15.12 Central Imaging Core Laboratory

A centralized imaging core laboratory will be used to review lesion at study entry, develop imaging acquisition protocols, and conduct imaging processing and analyses.

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 the study product or surgical procedure. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the study product or surgical procedure, whether or not considered related to the study product or surgical procedure. 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,
- inpatient hospitalization or prolongation of hospitalization,
- a persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions,
- 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)

If the subject develops an adverse event during the post-surgical hospitalization, the adverse event should be assessed as non-serious UNLESS the adverse event prolonged the hospital stay [beyond Visit 5], or resulted in one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious (medically important event).

A Product Technical Compliance (PTC) includes a failure or malfunction and any adverse reaction and/or any responses in recipients of manufacturers of human cells, tissues, and cellular and tissue-based products, regardless of manufactures, distribution, storage, or use/application.

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 **Suspected Adverse Reaction** is an AE for which there is a reasonable possibility that the study product or surgical procedure caused the AE. A reasonable possibility means there is evidence to suggest a causal relationship between the study product or surgical procedure and the AE.

A **Serious and Unexpected Suspected Adverse Reaction** (**SUSAR**) is any suspected adverse reaction to the study product or surgical procedure that is both serious and unexpected.

All SUSARs will be submitted as expedited reports to the applicable regulatory authorities/federal agencies. 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 Enrollment and ends 12 months after the administration of SB623.

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

16.3 Recording of AEs

All AEs, regardless of severity, seriousness, or presumed relationship to the study product or surgical procedure, 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 or Surgical Procedure

The Investigator must record his/her opinion concerning the relationship of the AE to the study product and the surgical procedure on the Adverse Event CRF. Table 4 below provides guidance for assigning relationship to study product or surgical procedure.

Table 4 Relationship of Adverse Event to Administration of the Study Product or Surgical Procedure

Unrelated	No temporal relationship to study product or surgical procedure, or the presence of a reasonable causal relationship to another drug, concurrent disease, or circumstance and the adverse event (AE).
Unlikely	A temporal relationship to study product or surgical procedure, but no reasonable causal relationship between study product or surgical procedure and the AE.
Possibly	A reasonable causal relationship between the study product or surgical procedure and the AE. Information related to withdrawal of cell treatment/procedure was lacking or unclear.
Probably	A reasonable causal relationship between the study product or surgical procedure and the AE. The event responded to withdrawal of cell treatment/procedure. Re-challenge was not required.
Definitely	A reasonable causal relationship between the study product or surgical procedure and the AE. The event responded to withdrawal of the cell treatment/procedure, and recurred with re-challenge, when clinically feasible.

16.5 Reporting Serious Adverse Events and Product Technical Compliances

Any Serious Adverse Event or PTC, 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 **within 24 hours after the site becomes aware of the event** to the Safety Monitor (ProPharma Group/PROSAR or designee).

The contact information for reporting SAEs is as follows for the US and Ukraine:

ProPharma/Group PROSAR
Email: clinicalsafety@propharmagroup.com
FAX: 866-681-1063

The contact information for reporting SAEs is as follows for Japan:

TBI-01safety@crodot.ip

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 or designate 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 of applicable regulatory authorities/federal agencies, other Investigators, IRBs, IBCs 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) and Institutional Biosafety Committee (IBC) in accordance with the EC/IRB/IBC by laws.

All additional follow-up evaluations of the SAE must be reported to ProPharma Group/PROSAR or designee 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 efficacy 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%, 75% and 100% of the total population.

18.0 STATISTICAL METHODS

18.1 Analysis Populations

18.1.1 Modified Intent-to-Treat Population

The Intent-to-Treat (ITT) population will include all randomized patients. All efficacy analyses will be conducted on modified ITT (mITT) population, which is defined as all randomized patients who complete the surgical procedure. In analyses based on the mITT population, subjects will be analyzed according to their randomized treatment assignment. Analyses based on the mITT population will be considered the primary analyses of efficacy.

18.1.2 Per Protocol Population

The Per Protocol (PP) population will include all randomized patients who have no major protocol violations. Major protocol violations will be identified based on blinded data after the study is completed, but before database lock and the unblinding of the treatment group assignments. All efficacy analyses will be repeated on this population. In analyses based on the PP population, subjects will be analyzed according to their randomized treatment assignment. Analyses based on the PP population will be considered secondary analyses of efficacy.

18.1.3 Safety Population

The safety population will include all study patients who undergo surgery (implant or sham). All safety analyses will utilize this population. In analyses based on the safety population, subjects will be analyzed according to the actual treatment received.

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 being locked and the treatment being unblinded.

In general, continuous variables will be summarized by the following descriptive statistics: sample size, mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized by frequencies and percentages (contingency tables). The three SB623 dose groups will be pooled for all analyses, except where noted otherwise.

18.2.1 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group using descriptive statistics for continuous variables and frequencies and percentages for categorical variables.

18.2.2 Analysis of Efficacy

All efficacy analyses will be performed on the mITT and PP populations. The efficacy endpoints are to be analyzed per the SAP.

18.2.2.1 Primary Efficacy Endpoint Analysis

The primary analysis will be a comparison of the mean change from baseline in the Fugl-Meyer Motor Scale score of SB623 treated subjects (pooling all SB623 doses) to sham surgical controls at 24 weeks. A mixed model repeated measures (MMRM) analysis will be performed with terms for treatment, visit, the baseline Fugl-Meyer Motor Scale score, the GOS-E score at screening, and the treatment-by-visit interaction. The Restricted Maximum Likelihood Estimation procedure will be employed using an unstructured covariance matrix. Missing observations will not be imputed.

18.2.2.2 Secondary Efficacy Endpoint Analyses

Secondary analyses will evaluate a number of outcomes:

A. Comparison of the mean change from baseline in the Disability Rating Scale (DRS) score of SB623 treated subjects (pooling all SB623 doses) to sham surgical controls at 24 weeks will be performed in a manner analogous to that for the primary efficacy endpoint.
B. Comparison of the mean change from baseline in the Action Research Arm Test (ARAT) total score of SB623 treated subjects (pooling all SB623 doses) to sham surgical controls at 24 weeks will be performed in a manner analogous to that for the primary efficacy endpoint. This analysis will be based on upper extremity deficit patients only.
C. Comparison of the mean change from baseline in Gait Velocity of SB623 treated subjects (pooling all SB623 doses) to sham surgical controls at 24 weeks will be performed in a manner analogous to that for the primary efficacy endpoint. This analysis will be based on lower extremity deficit patients only.
D. Comparison of the mean change from baseline in the two NeuroQOL subdomain T scores of SB623 treated subjects (pooling all SB623 doses) to sham surgical controls at 24 weeks will be performed in a manner analogous to that for the primary efficacy endpoint. The two subdomains include:
    a. Upper Extremity Function (Fine Motor ADL)
    b. Lower Extremity Function (Mobility)

    The analysis of the Upper Extremity Function domain will be based on upper extremity deficit patients only, and the analysis of the Lower Extremity Function domain will be based on lower extremity deficit patients only.
E. The proportion of SB623 treated subjects (pooling all 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 24 weeks (from Baseline) using a logistic regression model with treatment (SB623 vs. sham placebo), the baseline Fugl-Meyer Motor Scale score, and the GOS-E score at screening as terms in the model. The outcome variable of this analysis is a dichotomized variable based on of the Global Rating of Perceived Change score ($\geq$6 vs. <6).

In addition, each efficacy endpoint mentioned above will be analyzed to examine dose response. Similar statistical methodologies to those used to evaluate SB623 combined doses versus the surgical sham control will be used for each efficacy endpoint, except that dose will be included as a term in the model instead of treatment. Dose will be a continuous variable with the control treatment assigned a value of 0.

18.2.2.3 Exploratory Efficacy Analyses

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

18.2.2.4 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) will be summarized by presenting, for each treatment group, the number and percentage of patients having any adverse events, having an adverse event that led to

discontinuation from the study, having an adverse event in each System Organ Class (SOC) and having each individual type of adverse event (Preferred Term). These analyses will also be performed for serious adverse events (SAEs). Adverse events will also be summarized at the event level by severity, by relationship to study product or surgery, and by action taken. Other information collected will be listed. 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.

For each treatment group, descriptive statistics will be presented by visit for the actual values and the changes from baseline for each quantitative laboratory test. The difference between treatment groups in the mean change from baseline will also be presented. For each laboratory test and each treatment group, the one- sample t-test will be used to test whether the mean change from baseline equals 0 for each post-baseline time point. The two-sample t-test will be used to test whether the mean changes from baseline are equal for the two treatments. A shift table will summarize changes in status (normal, abnormal) from baseline to each post-baseline time point for each laboratory test, and abnormal lab values will be flagged in the data listings.

For each treatment group, descriptive statistics will be presented by visit for the actual values and the changes from baseline for each vital sign. The difference between treatment groups in the mean change from baseline will also be presented. For each vital sign and each treatment group, the one-sample t-test will be used to test whether the mean change from baseline equals 0 for each post-baseline time point. The two-sample t-test will be used to test whether the mean changes from baseline are equal for the two treatments. A shift table will summarize changes in status (normal, abnormal) from baseline to each post-baseline time point for each vital sign, and abnormal values will be flagged in the data listings.

18.4 Multiplicity Considerations

Multiplicity considerations will not be taken into consideration in the analyses for this Phase 2 study.

18.5 Missing Data

Every effort will be made to reduce the number of dropouts and to document reasons for dropping out. Missing data will be discussed in the Statistical Analysis Plan (SAP).

18.6 Determination of Sample Size

For a two-sample t-test to show superiority of SB623 over sham control, assuming 80% power, alpha of 0.05, a two-tailed test, and 3:1 randomization, a sample size of 48 (36 subjects in the treatment group and 12 subjects in the control group) is required. This assumes that the mean change from baseline to 24 weeks in the FM-Motor Scale score is 10.0 for the treatment group (pooling all SB623 doses) and 3.0 for the control group, with an assumed standard deviation of 7.25 in each group. Based on an 8% upward adjustment to compensate for dropout patients, a total of approximately 52 subjects will be required. Since the analysis of efficacy is to be based on the modified ITT population, subjects will continue to be enrolled in the study until there are a total of approximately 52 subjects in the mITT population. The vast majority of subjects will be from outside of Japan; however, a sufficient number of Japanese patients are to be enrolled in order to address Japanese regulatory requirements.

18.7 Interim Analysis

The primary efficacy end point is at 24 weeks. Therefore an interim analysis is planned after all randomized subjects who have not dropped out of the study have completed their 24 weeks visit to facilitate strategic discussion with regulatory agencies for future plans of the program.

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 clinical study report.

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)/Institutional Biosafety Committee (IBC)

The Investigator must submit the final protocol and proposed informed consent document to an Independent Ethics Committee (EC) or Institutional Review Board (IRB) and Institutional Biosafety Committee (IBC), where applicable, that complies with the ICH Guideline for Good Clinical Practice. The EC/IRB/IBC 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/IBC approval of the study protocol and the informed consent has been received.

Substantive modifications to the protocol will be submitted to the EC/IRB/IBC for approval. These modifications may be implemented only after EC/IRB/IBC 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/IBC 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/IBC for approval prior to implementing these documents.

The Investigator will make appropriate and timely reports to the EC/IRB/IBC as required by applicable government regulations and EC/IRB/IBC 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/IBC. 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/IBC in a timely fashion and to retain originals in a file. This EC/IRB/IBC 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 agreed upon on Section 19.5. Any deviation from the design of the study as set forth in this document must be recorded as a protocol deviation and be explained in detail as it occurs and/or is detected.

19.5 Protocol Modifications

Neither the Investigators nor the Sponsor will modify this protocol without obtaining the concurrence of the other. All protocol amendments will be issued by the Sponsor, and must be signed and dated by the Investigator prior to implementation of the amendment. The Sponsor will submit protocol modifications to Regulatory Agencies as required. The Investigator is responsible for notifying the EC/IRB/IBC of changes. Substantive changes will require EC/IRB/IBC 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/IBC 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 may capture the following information: patient number, initials, date of screen/enrollment, reason for not enrolling (if applicable), and any comments.

The results from Screening and data collected during the study (except clinical laboratory test

results) will be recorded in the subject's electronic CRF. The study sites will use an EDC system 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.

In compliance with remote data retention requirements, the study sites will be provided with a CD-ROM containing the CRFs and the complete audit trail in portable document format (PDF), subsequent to database lock.

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

19.7 Maintaining Records

A study binder must be maintained at the investigative site 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 or for the length of time required by the relevant national or local health authorities. No records may be disposed without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location. The study site must make available any records for inspection by applicable health authorities.

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.

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

19.8 Monitoring, Auditing, Inspecting

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

19.9 Confidentiality

The anonymity of patients participating in this study must be maintained. Patients will be identified by their assigned patient number and their initials in all written communications between the Investigator and Sponsor. Documents that are not submitted to the Sponsor and that identify the patient (e.g., signed informed consent; source documents/charts) will be made available to the Sponsor or regulatory authorities for inspections, but will be maintained in confidence.

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

19.10 Publication Policy

Publication of the results of this study may be appropriate. At least 30 days prior to expected submission to the intended publisher or meeting committee, the Investigator must submit a copy of the desired presentation (oral or written) or publication manuscript to the Sponsor. This review period may be shortened upon mutual consent where circumstances require expeditious review. The Sponsor reserves the right to suggest modification of any publication, presentation or use by the Investigator if such activity may jeopardize a patent application, an existing patent, or other proprietary rights. 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 following neurological injury. While many of these measures have been applied to patients recovering from stroke they are also used in the context of traumatic brain injury (TBI).[1-4] 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. 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.[5] Given that the focus of SB623 is to treat chronic TBI patients with persistent deficits in the *motor* domain of neurological function, the outcome measures we propose to use in our Phase 2 study include the following in addition to the global functional Disability Rating Scale which has been used extensively in the assessment of recovery from TBI[6-10]:

- 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 Domains (Secondary Endpoints) -
    - Upper Extremity Function
    - Lower Extremity Function

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

The Fugl-Meyer (F-M) scale was developed specifically because prior scales focused on Activities of Daily Living (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.[11] The F-M scale is now one of the most widely recognized and clinically relevant measures of body function impairment.[12] The motor component of the F-M scale in particular has well-established reliability and validity across different recovery time points.[11, 13]

The F-M scale assesses several dimensions of impairment, including range of motion, pain, sensation, upper extremity, lower extremity, and balance.[14] 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 upper extremity joints (shoulder, elbow, forearm, wrist, hand) and lower extremity joints (hip, knee, and ankle). The motor score ranges from 0 (hemiplegia) to a maximum of 100 points (normal motor performance).[11] The F-M motor component consists of the 33-item upper-extremity subscale (UE- FM) and the 17-item lower-extremity subscale (LE-FM).[14] The UE-FM ranges from 0 to 66[15] 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.

The F-M scale assesses several impairment dimensions and has been extensively used in studies with **chronic** motor deficit following neurological injury. In fact, in a systematic review of RCTs examining robot assisted therapy, 60% of the RCTs included in analysis used the F-M scale as the primary outcome parameter.[16] More recent RCTs investigating the use of patients continue to use the F-M motor scale as the primary outcome measure.[17-20] Other studies include constraint induced therapy trials[21, 22], brain-machine interface[23], transcutaneous electrical nerve stimulation (primary outcome measure)[24, 25] and mirror therapy (primary outcome measure in this 33 patient RCT).[26]

20.2 Justification for the use of the Disability Rating Scale (DRS)

The DRS has been commonly used to track recovery of an individual from coma to community and to measure general functional changes over the course of recovery for individuals with moderate to severe TBI.[27] It is a sensitive, functional, reliable, and quantitative means of monitoring patients with traumatic head injury during the course of their recovery.[6] It is an observer rated, 30 point continuous scale that evaluates eight areas of functioning in four categories:
(1) Consciousness (eye opening, verbal response, motor response)
(2) Cognitive ability (feeding, toileting, grooming)
(3) Dependence on others
(4) Employability
Each area of functioning is rated on a scale of 0 to either 3 or 5. The maximum score is 29 (extreme vegetative state) and the minimum score is 0 (person without disability).

Ceiling effects at discharge and at 1 year post injury are lower for the DRS than the Functional Independence Measure (FIM).[7, 27] DRS is also more sensitive to changes during a shorter time period than FIM and seems to be more appropriate for detecting long-term deficits.[10] However, it has also been noted that this instrument which measures global function may not be ideal at detecting meaningful changes year to year after TBI in contrast to narrow domain measures of disability.[10]

20.3 Rationale for Narrow Domain Outcome Measures in Chronic TBI Patients with Motor Deficit

The neurological deficit associated with TBI depends on the location, extent and pattern of resolution of the injury. 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.

Several narrow domain outcome measures have been devised, validated and applied to the assessment of clinical recovery following neurological injury. 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.[5]

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 TBI patients with motor deficits is provided below.

20.3.1 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.[3, 28, 29] 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).[30-35] 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.[36] The ARAT consists of 19 items grouped into four hierarchical subscales: grasp, grip, pinch, and gross movement.[37] Summation of a 0-3 score in each item yields a total score between 0 and 57.

20.3.2 Justification for use of Gait Velocity as a secondary endpoint

Gait is commonly affected in TBI[1, 2, 4, 38] and Gait Velocity is a useful outcome measure of lower extremity function as walking speed predicts the level of disability[39, 40] as improvements are correlated with better quality of life.[41] Furthermore, Gait Velocity measures are objective and have well defined thresholds.

20.3.3 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.[42] 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 a variety of 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.[43] In short, the validity of the NeuroQOL measures for adults with neurological impairment is supported with satisfactory internal consistency, test-retest reliability and significant correlations with many external validity measures.

20.3.3.1 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.[42] 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.

20.4 References

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21.0 APPENDIX B: WHO STANDARD TOXICITY CRITERIA

The WHO Standard Toxicity Criteria is tabulated below in Table 5.

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 5 WHO (World Health Organization) Toxicity Criteria by Grade

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Haematology	WBC ($x10^3$/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 ($x10^3$/l)	2	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
Haematology	Lymphocytes ($x10^3$/l)	2	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
Haematology	Haemorrhage	none	mild, no	gross, 1 - 2 units transfusion per episode	gross, 3 - 4 units transfusion per episode	massive, > 4 units transfusion per episode
Coagulation	Fibrinogen	WNL	0.99 - 0.75 x N	0.74 - 0.50 x N	0.49 - 0.25 x N	< 0.25 x N
Coagulation	Prothrombin time(Quick)	WNL	1.01 - 1.25 x N	1.26 - 1.50 x N	1.51 - 2.00 x N	> 2.00 x N
Coagulation	Partial thromboplastin time	WNL	1.01 - 1.66 x N	1.67 - 2.33 x N	2.34 - 3.00 x N	> 3.00 x N
Metabolic	Hyperglycaemia (mg/dl)	< 116	116 - 160	161 - 250	251 - 500	> 500 or ketoacidosis
Metabolic	Hypoglycaemia (mg/dl)	> 64	55 - 64	40 - 54	30 - 39	< 30
Metabolic	Amylase	WNL	< 1.5 x N	1.5 - 2.0 x N	2.1 - 5.0 N	> 5.0 x N
Metabolic	Hypercalcaemia (mg/dl)	< 10.6	10.6 - 11.5	11.6 - 12.5	12.6 - 13.4	13.5
Metabolic	Hypocalcaemia (mg/dl)	> 8.4	8.4 - 7.8	7.7 - 7.0	6.9 - 6.1	6

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Metabolic	Hypomagnesaemia (mg/dl)	> 1.4	1.4 - 1.2	1.1 - 0.9	0.8 - 0.6	0.5
Gastrointestinal	Nausea	none	able to eat reasonable intake	intake significantly decreased but can eat	no significant intake	—
Gastrointestinal	Vomiting	none	1 episode in 24 hrs	2 - 5 episodes in 24 hrs	6 - 10 episodes in 24 hrs	> 10 episodes in 24 hrs or requiring parenteral support
Gastrointestinal	Diarrhoea	none	increase of 2 - 3 stools / day over pre-Rx	increase of 4 - 6 stools / day, or nocturnal stools, or moderate cramping	increase of 7 - 9 stools / day, or incontinence, or severe cramping	increase of > 10 stools / day or grossly bloody diarrhoea, or need for parenteral support
Gastrointestinal	Stomatitis	none	painless ulcers, erythema, or mild soreness	painful erythema, oedema, or ulcers but can eat solids	painful erythema, oedema, or ulcers and cannot eat solids	requires parenteral or enteral support for alimentation
Liver	Bilirubin (N = 17 µmol/L)	WNL	-----	< 1.5 x N	1.5 - 3.0 x N	> 3.0 x N
Liver	Transaminase (SGOT, SGPT)	WNL	2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N
Liver	Alk Phos or 5 nucleotidase	WNL	< 2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N
Liver	Liver- clinical	No change from baseline	-----	-----	precoma	hepatic coma
Kidney, bladder	Creatinine	WNL	< 1.5 x N	1.5 - 3.0 x N	3.1 - 6.0 x N	> 6.0 x N
Kidney, bladder	Proteinuria	No change	1 (+) or < 0.3 g% or 3 g/L	2 - 3 (+) or 0.3 - 1.0 g% or 3 - 10 g/L	4 (+) or > 1.0 g% or > 10g/L	nephrotic syndrome
Kidney, bladder	Haematuria	Negative	microscopic only	gross, no clots no Rx needed	gross and clots bladder irrigation	requires transfusion or cystectomy
Kidney, bladder	Weight gain/ loss	< 5.0 %	5.0 - 9.9 %	10.0 - 19.9 %	20.00%	-----

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

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

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

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Fever of unknown origin	Fever of unknown origin	None	37.1° - 38.0° C 98.7° - 100.4° F	38.1° - 40.0° C 100.5° - 104° F	>40.0° C (>104° 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				
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, anticoagulant, or non-steroidal anti-inflammatory drugs during the conduct of this study will be in accordance with the American College of Chest Physicians 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 surgery
- 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 antiplatelet drugs (including non-steroidal anti-inflammatory drugs) 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 (LMWH) (*e.g.*, Lovenox).
- Anticoagulants (including antiplatelet or non-steroidal anti-inflammatory drugs) 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.[3]
- Other than patients at high risk of VTE, no antiplatelet, anticoagulant, 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.

[3] The decision to use bridging anticoagulation (*e.g.*, LMWH) should only be made by the attending surgeon where it is believed that the risks of VTE outweigh the risk of postoperative bleeding complications.

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