STATISTICAL ANALYSIS PLAN

Protocol # TBI-01

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)

Final Integrated Analysis Plan

September 16, 2019

Version 2.0

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Table of Contents

List of Tables

Table Number	Table Title
14.2.2.8	Secondary Efficacy Endpoints at Week 48 - Dose Response (Per Protocol Population)
14.2.3.1	Exploratory Efficacy Endpoints (mITT Population)
14.2.3.2	Exploratory Efficacy Endpoints (Per Protocol Population)
14.2.3.3	Exploratory Efficacy Endpoints - Dose Response (mITT Population)
14.2.3.4	Exploratory Efficacy Endpoints - Dose Response (Per Protocol Population)
14.2.4.1	Subgroup Analysis of Primary Efficacy Endpoint by Age at Informed Consent (mITT Population)
14.2.4.2	Subgroup Analysis of Primary Efficacy Endpoint by Gender (mITT Population)
14.2.4.3	Subgroup Analysis of Primary Efficacy Endpoint by GOS-E Score at Screening (mITT Population)
14.2.4.4	Subgroup Analysis of Primary Efficacy Endpoint by GOS-E Score at Screening (Per Protocol Population)
14.2.4.5	Subgroup Analysis of Primary Efficacy Endpoint by Baseline FMMS Score (mITT Population)
14.2.4.6	Subgroup Analysis of Primary Efficacy Endpoint by Baseline FMMS Score (Per Protocol Population)
14.2.4.7	Subgroup Analysis of Primary Efficacy Endpoint by Lot (mITT Population)
14.2.4.8	Subgroup Analysis of Primary Efficacy Endpoint by Percentage Cell Viability (mITT Population)
14.2.4.9	Effect of Anti-HLA Antibodies on Treatment Effect for Primary Efficacy Endpoint (mITT Population)
14.2.4.10	Relationship Between Anti-HLA Antibodies and Primary Efficacy Endpoint by Treatment Group (mITT Population)
14.2.5.1	Subgroup Analysis of Secondary Efficacy Endpoints by Age at Informed Consent (mITT Population)
14.2.5.2	Subgroup Analysis of Secondary Efficacy Endpoints by Gender (mITT Population)
14.2.5.3	Subgroup Analysis of Secondary Efficacy Endpoints by GOS-E Score at Screening (mITT Population)
14.2.5.4	Subgroup Analysis of Secondary Efficacy Endpoints by Baseline FMMS Score (mITT Population)
14.2.5.5	Subgroup Analysis of Secondary Efficacy Endpoints by Baseline FMMS Score (Per Protocol Population)
14.2.6.1	Fugl-Meyer Motor Scale (FMMS) (mITT Population)
14.2.6.2	Fugl-Meyer Motor Scale (FMMS) (Per Protocol Population)
14.2.7.1	Fugl-Meyer Motor Scale (FMMS) among Patients with both Upper and Lower Extremity Deficits (mITT Population)
14.2.7.2	Fugl-Meyer Motor Scale (FMMS) among Patients with both Upper and Lower Extremity Deficits (Per Protocol Population)
14.2.8.1	Fugl-Meyer Upper Extremity Subscale (UE-FM) Score among Upper Extremity Deficit Patients (mITT Population)
14.2.8.2	Fugl-Meyer Upper Extremity Subscale (UE-FM) Score among Upper Extremity Deficit Patients (Per Protocol Population)
14.2.9.1	Fugl-Meyer Lower Extremity Subscale (LE-FM) Score among Lower Extremity Deficit Patients (mITT Population)
14.2.9.2	Fugl-Meyer Lower Extremity Subscale (LE-FM) Score among Lower Extremity Deficit Patients (Per Protocol Population)

Table Number	Table Title
14.2.10.1	Disability Rating Scale (DRS) (mITT Population)
14.2.10.2	Disability Rating Scale (DRS) (Per Protocol Population)
14.2.11.1	Action Research Arm Test (ARAT) (mITT Population)
14.2.11.2	Action Research Arm Test (ARAT) (Per Protocol Population)
14.2.12.1	Gait Velocity (mITT Population)
14.2.12.2	Gait Velocity (Per Protocol Population)
14.2.12.3	Wilcoxon Rank Sum Analysis of Change from Baseline in Gait Velocity (mITT Population)
14.2.12.4	Gait Velocity: Shift Table for 10 Meter Walk Time Status (<300 Seconds vs. ≥ 300 Seconds) (mITT Population)
14.2.12.4	Gait Velocity: Shift Table for 10 Meter Walk Time Status (<300 Seconds vs. ≥ 300 Seconds) (mITT Population)
14.2.13.1	NeuroQOL (mITT Population)
14.2.13.2	NeuroQOL (Per Protocol Population)
14.2.14.1	Global Rating of Perceived Change from Baseline - Clinician (mITT Population)
14.2.14.2	Global Rating of Perceived Change from Baseline - Clinician (Per Protocol Population)
14.2.15.1	Global Rating of Perceived Change from Baseline - Subject (mITT Population)
14.2.15.2	Global Rating of Perceived Change from Baseline - Subject (Per Protocol Population)
14.2.16.1	Analysis of Primary and Secondary Efficacy Endpoints by Global Rating of Perceived Change from Baseline at Week 24 - Subject (GRPC-S) (mITT Population)
14.2.16.2	Analysis of Primary and Secondary Efficacy Endpoints by Global Rating of Perceived Change from Baseline at Week 24 - Subject (GRPC-S) (Per Protocol Population)
14.2.17.1	Analysis of Primary and Secondary Efficacy Endpoints by Global Rating of Perceived Change from Baseline at Week 24 - Clinician (GRPC-C) (mITT Population)
14.2.17.2	Analysis of Primary and Secondary Efficacy Endpoints by Global Rating of Perceived Change from Baseline at Week 24 - Clinician (GRPC-C) (Per Protocol Population)
14.2.18.1	Area Under the ROC Curve for Select Primary and Secondary Efficacy Endpoints Based on the Global Rating of Perceived Change from Baseline to Week 24 - Clinician (mITT Population)
14.2.18.2	Area Under the ROC Curve for Select Primary and Secondary Efficacy Endpoints Based on the Global Rating of Perceived Change from Baseline to Week 24 - Subject (mITT Population)
14.2.19	Test for Equality of Cumulative Distribution Functions (CDFs) (pooled SB623 vs. Control) of Select Primary and Secondary Efficacy Endpoints Based on the Kolmogorov-Smirnov Test (mITT Population)
14.2.20.1	Primary Efficacy Endpoint (Japan Versus Rest of the World) (mITT Population)
14.2.20.2	Primary Efficacy Endpoint - Dose Response (Japan Versus Rest of the World) (mITT Population)
14.2.22.1	Primary Efficacy Endpoint Stratified by Presence of BDNF Mutation (mITT Population)
14.2.22.2	Primary Efficacy Endpoint Stratified by APOE Genotype (mITT Population)
14.2.22.3	Primary Efficacy Endpoint - Dose Response Stratified by Presence of BDNF Mutation (mITT Population)
14.2.22.4	Primary Efficacy Endpoint - Dose Response Stratified by APOE Genotype (mITT Population)

Table Number	Table Title
14.2.23.1	Mean Change from Baseline in Fugl-Meyer Motor Scale (FMMS) Score Among All Patients Stratified by Presence of BDNF Mutation (mITT Population)
14.2.23.2	Mean Change from Baseline in Fugl-Meyer Motor Scale (FMMS) Score Among All Patients Stratified by APOE Genotype (mITT Population)
14.2.24.1	Primary Efficacy Endpoint Stratified by Presence of Pre-Existing Donor-Specific Antibodies (mITT Population)
14.2.24.2	Primary Efficacy Endpoint Stratified by Whether or Not the Patient Had a Significant Increase in Donor-Specific Antibodies at Any Post-Baseline Visit (mITT Population)
14.2.24.3	Primary Efficacy Endpoint Stratified by Whether or Not the Patient Had Either Pre-Existing Donor-Specific Antibodies or a Significant Increase in Donor-Specific Antibodies at Any Post-Baseline Visit (mITT Population)
14.2.24.4	Primary Efficacy Endpoint – Dose Response Stratified by Whether or Not the Patient Had Either Pre-Existing Donor-Specific Antibodies or a Significant Increase in Donor-Specific Antibodies at Any Post-Baseline Visit (mITT Population)
14.2.25.1	Mean Change from Baseline in Fugl-Meyer Motor Scale (FMMS) Score Among All Patients Stratified by Presence of Pre-Existing Donor-Specific Antibodies (mITT Population)
14.2.25.2	Mean Change from Baseline in Fugl-Meyer Motor Scale (FMMS) Score Among All Patients Stratified by Whether or Not the Patient Had a Significant Increase in Donor-Specific Antibodies at Any Post-Baseline Visit (mITT Population)
14.2.25.3	Mean Change from Baseline in Fugl-Meyer Motor Scale (FMMS) Score Among All Patients Stratified by Whether or Not the Patient Had Either Pre-Existing Donor-Specific Antibodies or a Significant Increase in Donor-Specific Antibodies at Any Post-Baseline Visit (mITT Population)
14.2.26.1	Immunogenicity Endpoints (Safety Population)
14.2.26.2	Shift Tables for Immunogenicity Endpoints (Safety Population)
14.2.26.3	Increase in Donor-Specific Antibodies (Safety Population)
14.2.27.1	Head MRI: Actual Values and Changes from Baseline (mITT Population)
14.2.27.2	Head MRI: Actual Values and Changes from Baseline - Dose Response (mITT Population)
14.2.28.1	Head MRI: Actual Values and Changes from Baseline Stratified by Presence of FLAIR Lesion at Day 8 (mITT Population)
14.2.28.2	Head MRI: Actual Values and Changes from Baseline Stratified by Presence of Enhancing Lesion at Day 8 (mITT Population)
14.2.29	Pearson Product Moment Correlation between Change from Baseline in Fugl-Meyer Motor Scale (FMMS) Score at Week 24 and Change from Baseline in Head MRI Variables (mITT Population)
14.2.21	Secondary Efficacy Endpoints (Japan Versus Rest of the World) (mITT Population)
14.2.30.1	Presence, Size and Location of FLAIR Lesion at Day 8 (mITT Population)
14.2.30.2	Presence of Enhancing Lesion at Day 8 (mITT Population)
14.2.31	Primary Efficacy Endpoint Stratified by Presence of FLAIR Lesion at Day 8 (mITT Population)
14.2.32.1	Average Daily Total Energy Expenditure (affected side) and Change from Baseline (mITT Population)
14.2.32.2	Average Daily Total Energy Expenditure (affected side) and Change from Baseline among Lower Extremity Deficit Patients (mITT Population)

Table Number	Table Title
14.2.32.3	Average Daily Total Energy Expenditure (non-affected side) and Change from Baseline (mITT Population)
14.2.33.1	Average Daily Total Energy Expenditure (affected side) and Change from Baseline: Dose Response (mITT Population)
14.2.33.2	Average Daily Total Energy Expenditure (affected side) and Change from Baseline among Lower Extremity Deficit Patients: Dose Response (mITT Population)
14.2.33.3	Average Daily Total Energy Expenditure (non-affected side) and Change from Baseline: Dose Response (mITT Population)
14.2.33.4	Average Daily Total Energy Expenditure (non-affected side) and Change from Baseline among Lower Extremity Deficit Patients: Dose Response (mITT Population)
14.2.34.1	Average Daily Activity Counts (affected side) and Change from Baseline (mITT Population)
14.2.34.2	Average Daily Activity Counts (affected side) and Change from Baseline among Lower Extremity Deficit Patients (mITT Population)
14.2.34.3	Average Daily Activity Counts (non-affected side) and Change from Baseline (mITT Population)
14.2.35.1	Average Daily Activity Counts (affected side) and Change from Baseline: Dose Response (mITT Population)
14.2.35.2	Average Daily Activity Counts (affected side) and Change from Baseline among Lower Extremity Deficit Patients: Dose Response (mITT Population)
14.2.35.3	Average Daily Activity Counts (non-affected side) and Change from Baseline: Dose Response (mITT Population)
14.2.36.1	Average Non-Sedentary Time (unit=minutes) per Day (affected side) and Change from Baseline (mITT Population)
14.2.36.2	Average Non-Sedentary Time (unit=minutes) per Day (affected side) and Change from Baseline among Lower Extremity Deficit Patients (mITT Population)
14.2.36.3	Average Non-Sedentary Time (unit=minutes) per Day (affected side) and Change from Baseline: Dose Response (mITT Population)
14.2.36.4	Average Non-Sedentary Time (unit=minutes) per Day (affected side) and Change from Baseline among Lower Extremity Deficit Patients: Dose Response (mITT Population)
14.2.37.1	Average Time (unit=minutes) of Moderate or Vigorous Activity per Day (affected side) and Change from Baseline (mITT Population)
14.2.37.2	Average Time (unit=minutes) of Moderate or Vigorous Activity per Day (affected side) and Change from Baseline among Lower Extremity Deficit Patients (mITT Population)
14.2.37.3	Average Time (unit=minutes) of Moderate or Vigorous Activity per Day (affected side) and Change from Baseline: Dose Response (mITT Population)
14.2.37.4	Average Time (unit=minutes) of Moderate or Vigorous Activity per Day (affected side) and Change from Baseline among Lower Extremity Deficit Patients: Dose Response (mITT Population)
14.2.38	Primary Efficacy Endpoint - SB623 5.0 vs Control (mITT Population)
14.2.39	Primary Efficacy Endpoint and Gender and Geographic Area (Japan vs Rest of World) (mITT Population)
14.2.40	Primary Efficacy Endpoint and Percent Cell Viability: SB623 Subjects (mITT Population)
14.2.41	FMMS Change from Baseline and GRPC Scores at Week 24: SB623 Subjects (mITT Population

Table Number	Table Title
14.2.42	FMMS Change from Baseline and Presence of Any Post Treatment Hematoma: SB623 Subjects (mITT Population)
14.2.43	Secondary Efficacy Endpoints - SB623 5.0 x 10^6 vs Control (mITT Population)
14.2.44	Disability Rating Scale Improvement at Week 24: SB623 5M vs Control and SB623 10M vs Control (mITT Population)
14.2.45	Disability Rating Scale Responder Rate at Week 24: SB623 5M vs Control and SB623 10M vs Control (mITT Population)
14.2.46	Change from Baseline in Gait Velocity (meters/second) at Week 24: Lower Extremity Deficit Patients
14.2.47	Subjects Scoring >= 6 on Both Global Rating of Perceived Change from Baseline Scales at Week 24: DRS Score (mITT Population)
14.3.1.1	Treatment Emergent Adverse Events (TEAEs): Overview (Safety Population)
14.3.1.2	Treatment Emergent Adverse Events (TEAEs): Incidence by System Organ Class and Preferred Term (Patient Level) (Safety Population)
14.3.1.3	Treatment Emergent Serious Adverse Events (TESAEs): Incidence by System Organ Class and Preferred Term (Patient Level) (Safety Population)
14.3.1.4	Treatment Emergent Adverse Events (TEAEs) by System Organ Class/Preferred Term and Severity (Event Level) (Safety Population)
14.3.1.5	Treatment Emergent Adverse Events (TEAEs) by System Organ Class/Preferred Term and Relationship to Study Product (Event Level) (Safety Population)
14.3.1.6	Treatment Emergent Adverse Events (TEAEs) by System Organ Class/Preferred Term and Relationship to Surgery (Event Level) (Safety Population)
14.3.1.7	Treatment Emergent Adverse Events (TEAEs) by System Organ Class/Preferred Term and Action Taken (Event Level) (Safety Population)
14.3.1.8.1	Treatment Emergent Adverse Events (TEAEs): Overview (Japan Versus Rest of the World) (Safety Population)
14.3.1.8.2	Treatment Emergent Adverse Events (TEAEs): Incidence by System Organ Class and Preferred Term (Patient Level) (Japan Versus Rest of the World) (Safety Population)
14.3.1.8.3	Treatment Emergent Adverse Events (TEAEs) by System Organ Class/Preferred Term and Relationship to Study Product (Event Level) (Japan Versus Rest of the World) (Safety Population)
14.3.1.8.4	Treatment Emergent Adverse Events (TEAEs) by System Organ Class/Preferred Term and Relationship to Surgery (Event Level) (Japan Versus Rest of the World) (Safety Population)
14.3.1.9	Treatment Emergent Serious Adverse Events (TESAEs): Incidence by System Organ Class and Preferred Term (Patient Level) (Japan Versus Rest of the World) (Safety Population)
14.3.1.10.1	Presence of Treatment Emergent Serious Adverse Events (SAEs) (Safety Population)
14.3.1.10.2	Number of Treatment Emergent Serious Adverse Events (SAEs) Per Patient (Safety Population)
14.3.1.11.1	Presence of Serious Adverse Events (SAEs) (Safety Population)
14.3.1.11.2	Number of Serious Adverse Events (SAEs) Per Patient (Safety Population)
14.3.1.12	Subdural Hematomas and Parenchymal Hematomas: Presence, Volume, and Status
14.3.4.1	Hematology: Actual Values and Changes from Baseline (Safety Population)
14.3.4.2	Hematology: Shift Table (Safety Population)
14.3.4.3	Serum Chemistry: Actual Values and Changes from Baseline (Safety Population)

Table Number	Table Title
14.3.4.4	Serum Chemistry: Shift Table (Safety Population)
14.3.4.5	International Normalized Ratio (INR): Actual Values and Changes From Baseline (Safety Population)
14.3.5.1	Vital Signs: Actual Values and Changes from Baseline (Safety Population)
14.3.5.2	Anti-HLA Antibodies (Safety Population)
14.3.5.3	Pearson Product Moment Correlation Between MFI and SB623 Dose (Safety Population)

List of Listings

Listing Number	Listing Title
16.2.1	Subject Completion Status (Consented Subjects)
16.2.2	Protocol Deviations (ITT Population)
16.2.3.1	Subject Eligibility (Consented Subjects)
16.2.3.2	Randomization and Analysis Populations (Consented Subjects)
16.2.3.3	Subjects Excluded from Per Protocol Population (ITT Population)
16.2.4.1	Demographics (ITT Population)
16.2.4.2	Subgroup Variables (ITT Population)
16.2.4.3	Medical History (ITT Population)
16.2.4.4	Body Size Measurements at Screening (Safety Population)
16.2.4.5	Pregnancy Test (ITT Population)
16.2.4.6	Occult Malignancy Assessment at Screening (ITT Population)
16.2.4.7	GOS-E Score and Motricity Index at Screening (ITT Population)
16.2.4.8	HLA Typing (ITT Population)
16.2.4.9	APOE4 & BDNF VAL66MET Genotyping (ITT Population)
16.2.4.10	Genotyping Variables (ITT Population)
16.2.4.11	Antibody Subgroup Variables (mITT Population)
16.2.5.1	Surgery (ITT Population)
16.2.5.2	Prior and Concomitant Medications (Safety Population)
16.2.6.1.1	Fugl-Meyer Motor Scale (FMMS) (Missing Individual FMMS Items at Baseline Imputed with 0) (ITT Population)
16.2.6.1.2	Fugl-Meyer Motor Scale (FMMS) (Missing Individual FMMS Items at Baseline Imputed with First Observed Post-Baseline Value) (ITT Population)
16.2.6.2	Action Research Arm Test (ARAT) (ITT Population)
16.2.6.3	Gait Velocity (ITT Population)
16.2.6.4	NeuroQOL (ITT Population)
16.2.6.5	Disability Rating Scale (ITT Population)
16.2.6.6	Global Rating of Perceived Change from Baseline - Clinician (ITT Population)
16.2.6.7	Global Rating of Perceived Change from Baseline - Subject (ITT Population)
16.2.6.8	Physical Therapy Exercise Diary (ITT Population)
16.2.6.9.1	Leg Activity Monitor Baseline Characteristics (mITT Population)
16.2.6.9.2	Leg Activity Monitor Average Values (mITT Population)
16.2.6.9.3	Leg Activity Monitor Average Values: Change from Baseline (mITT Population)
16.2.6.9.4	Leg Activity Monitor Daily Values (mITT Population)
16.2.6.10	Leg Activity Monitor Application/Reapplication (mITT Population)
16.2.7.1	Adverse Events (Safety Population)
16.2.7.2	Adverse Events Resulting in Death (Safety Population)
16.2.7.3	Serious Adverse Events (Safety Population)
16.2.7.4	Adverse Events Resulting in Discontinuation (Safety Population)

Listing Number	Listing Title
16.2.8.1	Hematology (Safety Population)
16.2.8.2	Serum Chemistry (Safety Population)
16.2.8.3	International Normalized Ratio (INR) (Safety Population)
16.2.8.4	Anti-HLA Antibodies (Safety Population)
16.2.8.5	PBMC Sample (Safety Population)
16.2.8.6	Diffusion Tensor Imaging (DTI) (ITT Population)
16.2.8.7	Vital Signs (Safety Population)
16.2.8.8	Physical Examination (Safety Population)
16.2.8.9	12-Lead ECG (Safety Population)
16.2.8.10	Chest X-Ray (Safety Population)
16.2.8.11	Head MRI (Safety Population)
16.2.8.12	Immunogenicity Endpoints (Safety Population)
16.2.8.13	Head MRI: General (ITT Population)
16.2.8.14	Head MRI Variables (ITT Population)
16.2.8.15	Post-Surgery (PS) FLAIR Lesion (ITT Population)
16.2.8.16	Subdural Hematomas, Parenchymal Hematomas and Diffuse Axonal Injury: Presence, Volume, and Status

List of Figures

Figure Number	Figure Title
14.2.7.2	Mean Change from Baseline in NeuroQOL Lower Extremity Function T Score Among Lower Extremity Deficit Patients: Dose Response (mITT Population)
14.2.7.3	Mean Change from Baseline in NeuroQOL Lower Extremity Function T Score Among Lower Extremity Deficit Patients (Per Protocol Population)
14.2.7.4	Mean Change from Baseline in NeuroQOL Lower Extremity Function T Score Among Lower Extremity Deficit Patients: Dose Response (Per Protocol Population)
14.2.8.1	Mean Global Rating of Perceived Change from Baseline Among All Patients - Clinician (mITT Population)
14.2.8.2	Mean Global Rating of Perceived Change from Baseline Among All Patients - Clinician: Dose Response (mITT Population)
14.2.9.1	Mean Global Rating of Perceived Change from Baseline Among All Patients - Subject (mITT Population)
14.2.9.2	Mean Global Rating of Perceived Change from Baseline Among All Patients - Subject: Dose Response (mITT Population)
14.2.10.1	Mean Change from Baseline in FMMS Score Among Patients with Both Upper and Lower Extremity Deficits (Missing Individual FMMS Items at Baseline Imputed with 0) (mITT Population)
14.2.10.2	Mean Change from Baseline in FMMS Score Among Patients with Both Upper and Lower Extremity Deficits: Dose Response (Missing Individual FMMS Items at Baseline Imputed with 0) (mITT Population)
14.2.10.3	Mean Change from Baseline in FMMS Score Among Patients with Both Upper and Lower Extremity Deficits (Missing Individual FMMS Items at Baseline Imputed with 0) (Per Protocol Population)
14.2.10.4	Mean Change from Baseline in FMMS Score Among Patients with Both Upper and Lower Extremity Deficits: Dose Response (Missing Individual FMMS Items at Baseline Imputed with 0) (Per Protocol Population)
14.2.11.1	ROC Curve for Change from Baseline to Week 24 in FMMS Score Among All Patients Based on Global Rating of Perceived Change from Baseline to Week 24 - Clinician (Missing Individual FMMS items at Baseline Imputed with 0) (mITT Population)
14.2.11.2	ROC Curve for Change from Baseline to Week 24 in ARAT Total Score Among Upper Extremity Deficit Patients Based on Global Rating of Perceived Change From Baseline to Week 24 - Clinician (mITT Population)
14.2.11.3	ROC Curve for Change from Baseline to Week 24 in Gait Velocity Among Lower Extremity Deficit Patients Based on Global Rating of Perceived Change From Baseline to Week 24 - Clinician (mITT Population)
14.2.11.4	ROC Curve for Change from Baseline to Week 24 in NeuroQOL Upper Extremity Function T Score Among Upper Extremity Deficit Patients Based on Global Rating of Perceived Change from Baseline to Week 24 - Clinician (mITT Population)
14.2.11.5	ROC Curve for Change from Baseline to Week 24 in NeuroQOL Lower Extremity Function T Score Among Lower Extremity Deficit Patients Based on Global Rating of Perceived Change from Baseline to Week 24 - Clinician (mITT Population)
14.2.12.1	ROC Curve for Change from Baseline to Week 24 in FMMS Score Among All Patients Based on Global Rating of Perceived Change from Baseline to Week 24 - Subject (Missing Individual FMMS Items at Baseline Imputed with 0) (mITT Population)

Figure Number	Figure Title
14.2.12.2	ROC Curve for Change from Baseline to Week 24 in ARAT Total Score Among Upper Extremity Deficit Patients Based on Global Rating of Perceived Change From Baseline to Week 24 - Subject (mITT Population)
14.2.12.3	ROC Curve for Change from Baseline to Week 24 in Gait Velocity Among Lower Extremity Deficit Patients Based on Global Rating of Perceived Change From Baseline to Week 24 – Subject (mITT Population)
14.2.12.4	ROC Curve for Change from Baseline to Week 24 in NeuroQOL Upper Extremity Function T Score Among Upper Extremity Deficit Patients Based on Global Rating of Perceived Change from Baseline to Week 24 - Subject (mITT Population)
14.2.12.5	ROC Curve for Change from Baseline to Week 24 in NeuroQOL Lower Extremity Function T Score Among Lower Extremity Deficit Patients Based on Global Rating of Perceived Change from Baseline to Week 24 - Subject (mITT Population)
14.2.13.1	Cumulative Distribution Function for Change from Baseline to Week 24 in FMMS Score Among All Patients (Missing Individual FMMS Items at Baseline Imputed with 0) (mITT Population) (mITT Population)
14.2.13.2	Cumulative Distribution Function for Change from Baseline to Week 24 in ARAT Total Score Among Upper Extremity Deficit Patients (mITT Population)
14.2.13.3	Cumulative Distribution Function for Change from Baseline to Week 24 in Gait Velocity Among Lower Extremity Deficit Patients (mITT Population)
14.2.13.4	Cumulative Distribution Function for Change from Baseline to Week 24 in NeuroQOL Upper Extremity Function T Score Among Upper Extremity Deficit Patients (mITT Population)
14.2.13.5	Cumulative Distribution Function for Change from Baseline to Week 24 in NeuroQOL Lower Extremity Function T Score Among Lower Extremity Deficit Patients (mITT Population)
14.2.14.1	Mean Change from Baseline in FMMS Score Among All Patients (Pooled SB623 vs. Control): Patients with BDNF Mutation (Missing Individual FMMS Items at Baseline Imputed with 0) (mITT Population)
14.2.14.2	Mean Change from Baseline in FMMS Score Among All Patients (Pooled SB623 vs. Control): Patients with No BDNF Mutation (Missing Individual FMMS Items at Baseline Imputed with 0) (mITT Population)
14.2.15.1	Mean Change from Baseline in FMMS Score Among All Patients (Pooled SB623 vs. Control): Patients with at Least One AP0E4 Allele (Missing Individual FMMS Items at Baseline Imputed with 0) (mITT Population)
14.2.15.2	Mean Change from Baseline in FMMS Score Among All Patients (Pooled SB623 vs. Control): Patients with No AP0E4 Alleles (Missing Individual FMMS Items at Baseline Imputed with 0) (mITT Population)
14.2.16.1	Mean Change from Baseline in FMMS Score Among All Patients (Pooled SB623 vs. Control): Patients with Pre-Existing Donor-Specific Antibodies (Missing Individual FMMS Items at Baseline Imputed with 0) (mITT Population)
14.2.16.2	Mean Change from Baseline in FMMS Score Among All Patients (Pooled SB623 vs. Control): Patients with No Pre-Existing Donor-Specific Antibodies (Missing Individual FMMS Items at Baseline Imputed with 0) (mITT Population)

Figure Number	Figure Title
14.2.17.1	Mean Change from Baseline in FMMS Score Among All Patients (Pooled SB623 vs. Control): Patients with Significant Increase in Donor-Specific Antibodies at Any Post-Baseline Visit (Missing Individual FMMS Items at Baseline Imputed with 0) (mITT Population)
14.2.17.2	Mean Change from Baseline in FMMS Score Among All Patients (Pooled SB623 vs. Control: Patients with No Significant Increase in Donor-Specific Antibodies at Any Post-Baseline Visit (Missing Individual FMMS Items at Baseline Imputed with 0) (mITT Population)
14.2.17.3	Mean Change from Baseline in FMMS Score Among All Patients (Pooled SB623 vs. Control): Patients with No Significant Increase in Donor-Specific Antibodies at Any Post-Baseline Visit (Missing Individual FMMS Items at Baseline Imputed with First Observed Post-Baseline Value) (mITT Population)
14.2.18.1	Mean Change from Baseline in FMMS Score Among All Patients (Pooled SB623 vs. Control): Patients with Either Pre-Existing Donor-Specific Antibodies or Significant Increase in Donor-Specific Antibodies at Any Post-Baseline Visit (Missing Individual FMMS Items at Baseline Imputed with 0) (mITT Population)
14.2.18.2	Mean Change from Baseline in FMMS Score Among All Patients (Pooled SB623 vs. Control): Patients with No Pre-Existing Donor-Specific Antibodies and No Significant Increase in Donor-Specific Antibodies at Any Post-Baseline Visit (Missing Individual FMMS Items at Baseline Imputed with 0) (mITT Population)
14.2.19.1	Mean Donor Antibody Specific MFI Value by Treatment Group (Pooled SB623 vs. Control): All Patients (Safety Population)
14.2.19.2	Mean Donor Antibody Specific MFI Value by SB623 Dose: All Patients (Safety Population)
14.2.20.1	Mean Donor Antibody Specific MFI Value by Treatment Group: Patients with Pre-Existing Donor-Specific Antibodies (Pooled SB623 vs. Control) (Safety Population)
14.2.20.2	Mean Donor Antibody Specific MFI Value by SB623 Dose: Patients with Pre-Existing Donor-Specific Antibodies (Safety Population)
14.2.21.1	Mean Donor Antibody Specific MFI Value by Treatment Group: Patients with No Pre-Existing Donor-Specific Antibodies (Pooled SB623 vs. Control) (Safety Population)
14.2.22.2	Mean Donor Antibody Specific MFI Value by SB623 Dose: Patients with No Pre-Existing Donor-Specific Antibodies (Safety Population)
14.2.23.1	Mean Change from Baseline in Average Daily Activity Count (affected side): Pooled SB623 vs. Control (mITT Population)
14.2.23.2	Mean Change from Baseline in Average Daily Activity Count (non-affected side): Pooled SB623 vs. Control (mITT Population)
14.2.24	Mean Change from Baseline in FMMS Score for Females and Males for SB623 (mITT Population)
14.2.25	Mean Change from Baseline in FMMS Score for GOS-E Categories for SB623 (mITT Population)
14.2.26	Mean Change from Baseline in FMMS Score for Age Groups for SB623 (mITT Population)
14.2.27	Mean Change from Baseline in FMMS Score for Lot A and Lot B for SB623 (mITT Population)
14.2.28	Mean Change from Baseline in FMMS Score for Percent Viability Groups for SB623 (mITT Population)

Figure Number	Figure Title
14.2.29	Mean Change from Baseline in FMMS Score for Pre-existing Donor-specific Antibodies Groups for SB623 (mITT Population)
14.2.30	Mean Change from Baseline in FMMS Score for BDNF Subgroups for SB623 (mITT Population)
14.2.31	Mean Change from Baseline in FMMS Score for ApoE4 Subgroups for SB623 (mITT Population)
14.2.32	Time Since Injury and Change in FMMS Score at 24 Weeks: Pooled SB623 vs Control (mITT Population)
14.2.33	Mean Change from Baseline in Disability Rating Scale: SB623 5M vs Control (mITT Population)
14.2.34	Mean Change from Baseline in Disability Rating Scale (Bar Chart): SB623 5M vs Control (mITT Population)
14.2.35.1	Cumulative Distribution Function for Change from Baseline to Week 24 in FMMS Score among All Patients (missing individual FMMS items at Baseline Imputed with 0) (mITT Population)
14.2.35.2	Cumulative Distribution Function for Change from Baseline to Week 24 in LE-FM Score among Upper Extremity Deficit Patients (missing individual FMMS items at Baseline Imputed with 0) (mITT Population)
14.2.35.3	Cumulative Distribution Function for Change from Baseline to Week 24 in LE-FM Score among Lower Extremity Deficit Patients (missing individual FMMS items at Baseline Imputed with 0) (mITT Population)
14.2.35.4	Cumulative Distribution Function for Change from Baseline to Week 24 in ARAT Total Score among Upper Extremity Deficit Patients (mITT Population)
14.2.35.5	Cumulative Distribution Function for Change from Baseline to Week 24 in Gait Velocity among Lower Extremity Deficit Patients (mITT Population)
14.2.35.6	Cumulative Distribution Function for Change from Baseline to Week 24 in NeuroQOL Upper Extremity Function T Score among Upper Extremity Deficit Patients (mITT Population)
14.2.35.7	Cumulative Distribution Function for Change from Baseline to Week 24 in NeuroQOL Lower Extremity Function T Score among Lower Extremity Deficit Patients (mITT Population)

1.0 INTRODUCTION

Six individual statistical analysis plans (SAPs) focused on different study areas were generated for the study entitled “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)".

The text from each of the six original SAPs as well as an addendum to the main study SAP are included in Appendices A though F for reference.

The analyses from the six SAPs have been combined into one set of comprehensive analyses numbered according to ICH conventions. This document provides the comprehensive numbering for the final CSR analyses.

2.0 REVISION HISTORY

Version No.	Date Issued	Author	Revision History
2.0	September 16, 2019	Susan Paadre	Integrate CSR tables, listings and figures from individual TBI-01 SAPs into one comprehensive set of outputs using ICH numbering. Provide one document that includes each individual SAP created for study TBI-01.

Appendix A:

TBI-01 MAIN STUDY STATISTICAL ANALYSIS PLAN AND ADDENDUM

STATISTICAL ANALYSIS PLAN

Protocol # TBI-01

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)

October 8, 2018

Version 1.0

Prepared for
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Study Number:	TBI-01
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)
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Version:	1.0

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San Bio TBI-01 SAP 20181008 Version 1.0

Table of Contents

List of Tables

Number	Title
5.3.2	Action Research Arm Test (ARAT) (Per Protocol Population)
5.4.1	Gait Velocity (mITT Population)
5.4.2	Gait Velocity (Per Protocol Population)
5.4.3	Wilcoxon Rank Sum Analysis of Change from Baseline in Gait Velocity (mITT Population)
5.4.4	Gait Velocity: Shift Table for 10 Meter Walk Time Status (< 300 Seconds vs. ≥ 300 Seconds) (mITT Population)
5.5.1	NeuroQOL (mITT Population)
5.5.2	NeuroQOL (Per Protocol Population)
5.6.1	Global Rating of Perceived Change from Baseline - Clinician (mITT Population)
5.6.2	Global Rating of Perceived Change from Baseline - Clinician (Per Protocol Population)
5.7.1	Global Rating of Perceived Change from Baseline - Subject (mITT Population)
5.7.2	Global Rating of Perceived Change from Baseline - Subject (Per Protocol Population)
5.8.1	Analysis of Primary and Secondary Efficacy Endpoints by Global Rating of Perceived Change from Baseline at Week 24 - Subject (GRPC-S) (mITT Population)
5.8.2	Analysis of Primary and Secondary Efficacy Endpoints by Global Rating of Perceived Change from Baseline at Week 24 - Subject (GRPC-S) (Per Protocol Population)
5.9.1	Analysis of Primary and Secondary Efficacy Endpoints by Global Rating of Perceived Change from Baseline at Week 24 - Clinician (GRPC-C) (mITT Population)
5.9.2	Analysis of Primary and Secondary Efficacy Endpoints by Global Rating of Perceived Change from Baseline at Week 24 - Clinician (GRPC-C) (Per Protocol Population)
5.10.1	Area Under the ROC Curve for Select Primary and Secondary Efficacy Endpoints Based on the Global Rating of Perceived Change from Baseline to Week 24 - Clinician (mITT Population)
5.10.2	Area Under the ROC Curve for Select Primary and Secondary Efficacy Endpoints Based on the Global Rating of Perceived Change from Baseline to Week 24 - Subject (mITT Population)
5.11	Test for Equality of Cumulative Distribution Functions (CDFs) (pooled SB623 vs. Control) of Select Primary and Secondary Efficacy Endpoints Based on the Kolmogorov-Smirnov Test (mITT Population)
6.1	Treatment Emergent Adverse Events (TEAEs): Overview (Safety Population)
6.2	Treatment Emergent Adverse Events (TEAEs): Incidence by System Organ Class and Preferred Term (Patient Level) (Safety Population)
6.3	Treatment Emergent Serious Adverse Events (TESAEs): Incidence by System Organ Class and Preferred Term (Patient Level) (Safety Population)
6.4	Treatment Emergent Adverse Events (TEAEs) by System Organ Class/Preferred Term and Severity (Event Level) (Safety Population)

Number	Title
6.5	Treatment Emergent Adverse Events (TEAEs) by System Organ Class/Preferred Term and Relationship to Study Product (Event Level) (Safety Population)
6.6	Treatment Emergent Adverse Events (TEAEs) by System Organ Class/Preferred Term and Relationship to Surgery (Event Level) (Safety Population)
6.7	Treatment Emergent Adverse Events (TEAEs) by System Organ Class/Preferred Term and Action Taken (Event Level) (Safety Population)
7.1	Hematology: Actual Values and Changes from Baseline (Safety Population)
7.2	Hematology: Shift Table (Safety Population)
7.3	Serum Chemistry: Actual Values and Changes from Baseline (Safety Population)
7.4	Serum Chemistry: Shift Table (Safety Population)
8	Vital Signs: Actual Values and Changes from Baseline (Safety Population)
9	International Normalized Ratio (INR): Actual Values and Changes from Baseline (Safety Population)
10	Concomitant Medications (Safety Population)
11	Anti-HLA Antibodies (Safety Population)

List of Listings

List of Figures

Number	Title
2.9.1.1	Mean Change from Baseline in UE-FM Score among Upper Extremity Deficit Patients (missing individual FMMS items at Baseline imputed with 0) (mITT Population)
2.9.1.2	Mean Change from Baseline in UE-FM Score among Upper Extremity Deficit Patients: Dose Response (missing individual FMMS items at Baseline imputed with 0) (mITT Population)
2.9.2.1	Mean Change from Baseline in UE-FM Score among Upper Extremity Deficit Patients (missing individual FMMS items at Baseline imputed with first observed post-baseline value) (mITT Population)
2.9.2.2	Mean Change from Baseline in UE-FM Score among Upper Extremity Deficit Patients: Dose Response (missing individual FMMS items at Baseline imputed with first observed post-baseline value) (mITT Population)
2.9.3.1	Mean Change from Baseline in UE-FM Score among Upper Extremity Deficit Patients (missing individual FMMS items at Baseline imputed with 0) (Per Protocol Population)
2.9.3.2	Mean Change from Baseline in UE-FM Score among Upper Extremity Deficit Patients: Dose Response (missing individual FMMS items at Baseline imputed with 0) (Per Protocol Population)
2.9.4.1	Mean Change from Baseline in UE-FM Score among Upper Extremity Deficit Patients (missing individual FMMS items at Baseline imputed with first observed post-baseline value) (Per Protocol Population)
2.9.4.2	Mean Change from Baseline in UE-FM Score among Upper Extremity Deficit Patients: Dose Response (missing individual FMMS items at Baseline imputed with first observed post-baseline value) (Per Protocol Population)
2.10.1.1	Mean Change from Baseline in LE-FM Score among Lower Extremity Deficit Patients (missing individual FMMS items at Baseline imputed with 0) (mITT Population)
2.10.1.2	Mean Change from Baseline in LE-FM Score among Lower Extremity Deficit Patients: Dose Response (missing individual FMMS items at Baseline imputed with 0) (mITT Population)
2.10.2.1	Mean Change from Baseline in LE-FM Score among Lower Extremity Deficit Patients (missing individual FMMS items at Baseline imputed with first observed post-baseline value) (mITT Population)
2.10.2.2	Mean Change from Baseline in LE-FM Score among Lower Extremity Deficit Patients: Dose Response (missing individual FMMS items at Baseline imputed with first observed post-baseline value) (mITT Population)
2.10.3.1	Mean Change from Baseline in LE-FM Score among Lower Extremity Deficit Patients (missing individual FMMS items at Baseline imputed with 0) (Per Protocol Population)
2.10.3.2	Mean Change from Baseline in LE-FM Score among Lower Extremity Deficit Patients: Dose Response (missing individual FMMS items at Baseline imputed with 0) (Per Protocol Population)

List of Abbreviations

ADL	Activities of Daily Living
AE	Adverse Event
ARAT	Action Research Arm Test
AUC	Area Under the Curve
BMI	Body Mass Index
CDF	Cumulative Distribution Function
CSPG	Chondroitin Sulphate Proteoglycans
CT	Computerized Tomography
DRS	Disability Rating Scale
DSMB	Data and Safety Monitoring Board
DTI	Diffusion Tensor Imaging
ECG	Electrocardiogram
FMMS	Fugl-Meyer Motor Scale
GMP	Good Manufacturing Practices
GOS-E	Glasgow Outcome Scale - Extended
GRPC-C	Global Rating of Perceived Change - Clinician
GRPC-S	Global Rating of Perceived Change - Subject
IND	Investigational New Drug
INR	International Normalized Ratio
ITT	Intent-to-Treat
IXRS	Interactive Web/Voice Response System
LE-FM	Fugl-Meyer Lower Extremity Subscale
LSM	Least-Squares Mean
MASC	Marrow Stromal Cells
MMRM	Mixed Model Repeated Measures
MRI	Magnetic Resonance Imaging
OR	Operating Room
PP	Per Protocol
REML	Restricted Maximum Likelihood Estimation
ROC	Receiver Operating Characteristic
SAE	Serious Adverse Event
SAS	Statistical Analysis System
TBI	Traumatic Brain Injury
UE-FM	Fugl-Meyer Upper Extremity Subscale
WHO	World Health Organization

1.0 INTRODUCTION

This document details the analysis plan for the study entitled "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)". It describes the proposed efficacy and safety analyses, including planned summary tables and by-subject data listings.

Traumatic brain injury (TBI) results from a sudden and external physical impact to the head and often leads to motor impairment (e.g., loss of ambulation, balance, coordination, fine motor skills, strength, and endurance) and cognitive impairment (e.g., loss of communication, information processing, memory, and perceptual skills). 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]

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.[10] Cell transplantation has already shown promise in the clinic for treating severe TBI[11], 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.[12] 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[13,14] and contribute to neurogenesis that occurs throughout adult mammalian life in the olfactory and hippocampal

regions.[7,13] Furthermore, the rate of neuro- and gliogenesis increases following injury.[7,8,9,13] 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.[15] Transplantation of primary neural stem cells has been shown to improve functional recovery following experimental TBI.[16,17,18]

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).[19] 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[20,21] or in vivo[22,23] environments. Mesenchymal stem cells are also known to produce a variety of trophic factors that may be beneficial to the injured and regenerating brain.[24,25] Transplantation of mesenchymal stem cells has been shown to improve functional recovery following experimental TBI.[26]

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 Good Manufacturing Practice (GMP) conditions by the transient transfection of bone marrow stromal cells (MASC) with a plasmid encoding the human Notch-1 intracellular domain.[27] This transfection is considered transient because the plasmid rapidly disappears with further expansion/passaging of the cells. Thus, the gene and its products, which were initially detected at very low levels, are not expected to be present at all after a short time post-implantation.

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

2.0 STUDY 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.

The primary objective of this study is to evaluate the clinical efficacy of intracranial administration of SB623 cells.

The secondary objectives of this study are as follows:

- 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.

3.0 STUDY DESIGN

3.1 Overview

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., United States), Eastern Europe (i.e., Ukraine), and Asia Pacific (i.e., Japan).

Table 1 below lists the procedures to be followed throughout the course of the study.

Table 1 Schedule of Assessments

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[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] Mandatory for subjects in US and Japan only

[2] Height and weight should be collected

1.2 and APTT >38 seconds).
[8] Head CT on Day 1 is post-operative.

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[14,15]	X[14,15]	X[14,15]
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 includes assessment site efficacy assessor who does not have access to patient study safety information because CGIC is a component of secondary endpoint and secure 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.

Table 1 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[14,15]	X[14,15]
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.

3.2 Method of Assigning Subjects to Treatment

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 million, 5 million, or 10 million SB623 cells. Randomization will be performed via an interactive web/voice response system (IXRS). For subjects in the United States 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.

3.3 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 of the protocol, 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.

3.4 Determination of Sample Size

For a two-sample t-test to show superiority of SB623 over sham surgery 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 Week 24 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.

3.5 Changes to the Protocol-Specified Analyses

An As Treated Population was added to the analysis populations.

The protocol stated that a mixed model repeated measures (MMRM) analysis with terms for treatment, visit, the baseline Fugl-Meyer Motor Scale score, the GOS-E score at screening, and the treatment-by-visit interaction would be performed for the primary efficacy endpoint. The model has been revised to now include terms for the baseline Fugl-Meyer Motor Scale score-by-visit interaction and the GOS-E score at screening-by-visit interaction.

The protocol stated that the following secondary efficacy endpoints would be analyzed in a manner analogous to that for the primary efficacy endpoint: the change from baseline in the Disability Rating Scale (DRS) score at Week 24, the change from baseline in the Action Research Arm Test (ARAT) total score at Week 24, the change from baseline in Gait Velocity at Week 24, and the change from baseline at Week 24 in the two NeuroQOL subdomain T scores (Upper Extremity Function (Fine Motor ADL) and Lower Extremity Function (Mobility)). Thus, the protocol specified model did not include terms for the baseline value of the endpoint-by-visit interaction or the GOS-E score at screening-by-visit interaction. These terms were added to the model for each of these endpoints.

The protocol stated that the primary efficacy endpoint and each of the above mentioned secondary efficacy endpoints would be analyzed to examine dose response, and that similar statistical methodology to that used to evaluate the SB623 combined doses vs. the sham surgery control treatment would be used, except that dose would be used instead of treatment and dose would be a continuous variable with the control treatment assigned a value of 0. Instead the MMRM analysis will be performed using a model with terms for visit, the interaction between SB623 dose and an indicator variable for the Week 4 visit, the interaction between SB623 dose and an indicator variable for the Week 12 visit, the interaction between SB623 dose and an indicator variable for the Week 24 visit, the baseline value of the endpoint, the baseline value of the endpoint-by-visit interaction, the GOS-E score at screening, and the GOS-E score at screening-by-visit interaction. The control treatment will not be included in this analysis.

4.0 EFFICACY AND SAFETY ENDPOINTS

For the mITT Population (see Section 6.1), patients with a Motricity Index UE Scale score at Screening of 10-81 will be considered to have an upper extremity deficit. 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 (see Section 6.2), 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. Patients with a LE Scale score at Screening 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.

4.1 Primary Efficacy Endpoint

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

4.2 Secondary Efficacy Endpoints

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 (the affected side will be analyzed) among upper extremity deficit patients
- Change from baseline in Gait Velocity (10 meter walk time in seconds) at Week 24 (the better of the two trials at the visit will be used for analysis) among lower extremity deficit patients
- Change from baseline at Week 24 in T scores of NeuroQOL sub-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

The ARAT total score is the sum of the scores from 19 tests spread across 4 subscales: grasp, grip, pinch, and gross movement. Each test is scored on an ordinal 4-point scale with 0=non movement, 1=the movement task is partially performed, 2=the movement task is completed but takes abnormally long, and 3=the movement is performed normally. If the score on the first test in a subscale = 3, then the score for that subscale is the maximum possible score (i.e., 3*number of tests). For the Gross Movement subscale, if the score on the first test = 0, then the score for that subscale = 0. For all other subscales, if the score on the first test does not equal 3 and the score on the second test = 0, then the score for that subscale = 0.

Items for the Neuro QOL Fine Motor ADL and Mobility subdomains are scored on an ordinal 5-point scale with 1=unable to do, 2=with much difficulty, 3=with some difficulty, 4=with a little difficulty, and 5=without any difficulty. The subdomain scores are the sum of the scores for the given domain. The Fine Motor ADL and Mobility raw scores are transformed to T-scores using tables 2 and 3, respectively.

Table 2 Adult Upper Extremity Function - Fine Motor, ADL

Upper Extremity Function – Fine Motor, ADL 8-item Short Form (Adult)					
Raw Score	T-Score	SE	Raw Score	T-Score	SE
8	12.8	2.0	25	27.3	2.0
9	13.7	2.3	26	28.0	2.0
10	14.7	2.4	27	28.7	2.0
11	15.8	2.5	28	29.5	2.0
12	16.9	2.4	29	30.2	2.1
13	18.0	2.4	30	30.9	2.1
14	19.0	2.3	31	31.7	2.1
15	19.9	2.2	32	32.6	2.2
16	20.8	2.1	33	33.5	2.3
17	21.6	2.1	34	34.5	2.4
18	22.4	2.1	35	35.6	2.7
19	23.1	2.0	36	37.1	3.2
20	23.9	2.0	37	39.3	4.2
21	24.6	2.0	38	41.2	4.5
22	25.3	2.0	39	43.7	4.7
23	26.0	2.0	40	53.8	7.8
24	26.7	2.0			

Table 3 Adult Lower Extremity Function - Mobility

Lower Extremity Function - Mobility 8-item Short Form (Adult)					
Raw Score	T-Score	SE	Raw Score	T-Score	SE
8	16.5	3.0	25	35.2	2.1
9	19.2	2.8	26	36.0	2.1
10	21.1	2.6	27	36.7	2.1
11	22.6	2.4	28	37.5	2.1
12	23.9	2.3	29	38.3	2.1
13	25.1	2.3	30	39.1	2.2
14	26.2	2.2	31	39.9	2.2
15	27.2	2.2	32	40.8	2.3
16	28.1	2.1	33	41.7	2.4
17	29.0	2.1	34	42.8	2.5
18	29.9	2.1	35	43.9	2.6
19	30.7	2.1	36	45.2	2.9
20	31.5	2.1	37	46.7	3.1
21	32.2	2.1	38	48.6	3.3
22	33.0	2.1	39	51.2	3.8
23	33.7	2.0	40	58.6	6.4
24	34.5	2.1			

4.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are as follows:

1. Change from baseline in Fugl-Meyer Motor Scale (FMMS) score at Week 24 among patients with both upper and lower extremity deficits
2. Change from baseline in Fugl-Meyer Motor upper-extremity subscale (UE-FM) score at Week 24 among upper extremity deficit patients
3. Change from baseline in Fugl-Meyer Motor lower-extremity subscale (LE-FM) score at Week 24 among lower extremity deficit patients
4. Improvement by ≥6 points at Week 24 from Baseline in UE-FM score among upper extremity deficit patients
5. Improvement by ≥3 points at Week 24 from Baseline in LE-FM score among lower extremity deficit patients
6. Improvement from Baseline by ≥10 points at Week 24 in Fugl-Meyer Motor Scale (FMMS) score among all patients
7. Improvement from Baseline by ≥6 points at Week 24 in Action Research Arm Test (ARAT) score among upper extremity deficit patients
8. Improvement from Baseline 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 in Gait Velocity on standard 10 m walk among lower extremity deficit patients
9. Pre- and post-contrast standard T1 and T2 weighted, dual echo, and FLAIR-MRI among all patients
10. Perfusion MRI among all patients
11. Diffusion tensor imaging (DTI) with tractography among all patients
12. Lower limb motion as measured by leg activity monitor among lower extremity deficit patients (applicable for US and Japan only)
13. Outcome analysis among all patients based on genotyping of polymorphisms at 3 specific loci:
    - HLA – degree of donor/recipient mismatch
    - BDNF Val66Met mutation present (yes/no)
    - ApoE (i.e., homo and heterozygosity for ApoE2, ApoE3, ApoE4 alleles)

4.4 Safety Endpoints

The safety endpoints are as follows:

- 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, and physical examination
- Changes in serum antibodies to SB623 over time

5.0 STATISTICAL CONSIDERATIONS

5.1 General Methodology

The statistical analysis of the data obtained from this study will be performed using SAS® version 9.4 or higher. All statistical tests will be performed at the 0.05 significance level.

The data collected in this study will be documented using summary tables and subject data listings. Continuous variables will be summarized using descriptive statistics, specifically the number of observations, mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized by frequencies and percentages. For the most part results will be presented for the four treatment groups separately and the three SB623 dose groups pooled. The three SB623 dose groups will be pooled for all statistical tests comparing SB623 to sham surgery, except where noted otherwise (i.e., dose response analyses).

Data listings will be sorted by center and subject ID. All date fields will be presented in a format of ddmmmyyyy (i.e., 01Jan2018) in the listings.

5.2 Adjustments for Covariates

A mixed model repeated measures (MMRM) analysis with adjustment for the baseline value of the endpoint and the GOS-E score at screening as continuous covariates as well as the corresponding baseline-by-visit and GOS-E score at screening-by-visit interaction terms will be used to analyze the following endpoints:

- The primary efficacy endpoint, the change from baseline in the Fugl-Meyer Motor Scale (FMMS) score at Week 24 among all patients
- Change from baseline in the Disability Rating Scale (DRS) score at Week 24 among all patients
- Change from baseline in the 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 at Week 24 in the two NeuroQOL subdomain T scores (Upper Extremity Function (Fine Motor ADL) and Lower Extremity Function (Mobility)) among upper and lower extremity deficit patients, respectively
- 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.

The endpoints mentioned above will be analyzed to examine dose response using a MMRM model with adjustment for the baseline value of the endpoint and the GOS-E score at screening as continuous covariates as well as the corresponding baseline-by-visit and GOS-E score at screening-by-visit interaction terms.

The primary efficacy endpoint will also be analyzed using an analysis of covariance model with adjustment for the presence of prior (i.e., at baseline) antibodies to donor cell HLA antigens, the interaction between treatment and the presence of prior antibodies to donor cell HLA antigens, the baseline FMMS score, and the GOS-E score at screening.

The proportions 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 (from Baseline) - Subject at Week 24 and on the Global Rating of Perceived Change (from Baseline) - Clinician at Week 24 will be compared to the corresponding proportions of sham surgery control subjects using logistic regression models with adjustment for the baseline Fugl-Meyer Motor Scale score and the GOS-E score at screening as continuous covariates.

The fourth, fifth, sixth, seventh, and eighth exploratory efficacy endpoints will be summarized using frequencies and percentages and will be analyzed using a logistic regression model with adjustment for the baseline value of the endpoint and the GOS-E score at screening as continuous covariates.

5.3 Handling of Dropouts and Missing Data

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

For FMMS score, the following imputation rules will be followed for missing data:

a) Impute missing individual items at post-baseline visits using the Last-Observation-Carried-forward (LOCF) method.
b) Impute missing individual items at baseline in the following two ways (i. imputed with a score of 0; ii. imputed with the first observed post-baseline value).

If there are no missing individual items for FMMS score at baseline, then the FMMS results will be shown only once, rather than once for each case specified in b) above.

5.4 Interim Analysis

The primary efficacy endpoint 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.

5.5 Multicenter Study

Approximately 52 subjects will be randomized into the study at approximately thirty (30) sites in North America (i.e., United States), Eastern Europe (i.e., Ukraine), and Asia Pacific (i.e., Japan). A maximum of 12 subjects will be enrolled at each Assessment site, and a maximum of 16 subjects will be enrolled or treated at each Surgery or Comprehensive site, respectively.

5.6 Multiple Comparisons / Multiplicity

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

5.7 Examination of Subgroups

Analyses of the primary and secondary efficacy endpoints will be performed on the following subgroups of interest:

- Age at Informed Consent (18-<50 years of age, 50-75 years of age)
- Gender
- GOS-E score at screening (3, 4, 5, or 6)
- Baseline FMMS score (0-50, 51-100)

The primary efficacy endpoint will also be analyzed by lot and by percentage cell viability (≤ sample median value vs. > sample median value). These subgroup analyses will be done for only the SB623 doses.

Analyses may also be performed on other subgroups of interest.

6.0 ANALYSIS POPULATIONS

6.1 Modified Intent-to-Treat Population

The Intent-to-Treat (ITT) population will include all randomized patients. All efficacy analyses will be conducted on the 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.

6.2 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.

6.3 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.

6.4 As Treated Population

The As Treated population will include all randomized patients who undergo surgery (implant or sham). In the event that a patient in the ITT population does not receive the treatment to which he/she was randomized (i.e., either no treatment or the wrong treatment), all efficacy analyses will be repeated on this population. Otherwise, no analyses will be performed on this population, because the analyses will be the same as for the ITT population. Therefore, no table shells will be produced for this population. In analyses based on the As Treated population, subjects will be analyzed according to the actual treatment received.

7.0 SUBJECT DISPOSITION

The numbers and percentages (based upon the ITT Population) of patients in the ITT Population, in the mITT Population, in the PP Population, in the Safety Population, in the As Treated Population, who completed the study, and who discontinued from the study before completion will be presented. For subjects who discontinued from the study before completion, the primary reason for early termination will be summarized using frequencies and percentages. For screen failures, the reason for screen failure will be summarized using frequencies and percentages.

8.0 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Subject demographic and body size measurements collected at the screening visit will be summarized using descriptive statistics for continuous variables (age at informed consent, height, weight, and BMI) and frequencies and percentages for categorical variables (sex, race, and ethnicity).

Medical history will be summarized by MedDRA system organ class (SOC) and Preferred Term using frequencies and percentages.

The GOS-E score, the Upper Extremity Scale Motricity Index, and the Lower Extremity Scale Motricity Index at screening will be summarized using descriptive statistics. The GOS-E score will also be summarized using counts and percentages.

HLA typing and ApoE4 and BDNF Val66Met genotyping will be summarized using counts and percentages.

9.0 SURGICAL PROCEDURE

Surgical procedure characteristics will be summarized using descriptive statistics or frequencies and percentages, as appropriate.

10.0 EFFICACY ANALYSES

10.1 Primary Efficacy Endpoint

The primary analysis will be a comparison of the least-squares mean (LSM) change from baseline in the Fugl-Meyer Motor Scale score of SB623 treated subjects (pooling all SB623 doses) to sham surgery control subjects at Week 24. A mixed model repeated measures (MMRM) analysis will be performed with terms for treatment (SB623 or sham surgery), visit, the treatment-by-visit interaction, the baseline Fugl-Meyer Motor Scale score, the baseline Fugl-Meyer Motor Scale score-by-visit interaction, the GOS-E score at screening, and the GOS-E score at screening-by-visit interaction. The Restricted Maximum Likelihood Estimation (REML) procedure will be employed using an unstructured covariance matrix. The LSM and standard error will be presented for the two treatments, together with a 95% confidence interval for the LSM. The difference in LSMs between treatments and corresponding 95% confidence interval will also be presented, together with the p-value from a two-sided, two-sample t-test based on the MMRM analysis, testing the null hypothesis that the LSMs for the two treatments are equal.

In addition, the primary efficacy endpoint, the change from baseline in the FMMS score at Week 24, will be analyzed to examine dose response. As for the primary analysis, a mixed model repeated measures (MMRM) analysis will be performed. The model will include terms for visit, the interaction between SB623 dose and an indicator variable for the Week 4 visit, the interaction between SB623 dose and an indicator variable for the Week 12 visit, the interaction between SB623 dose and an indicator variable for the Week 24 visit, the baseline Fugl-Meyer Motor Scale score, the baseline Fugl-Meyer Motor Scale score-by-visit interaction, the GOS-E score at screening, and the GOS-E score at screening-by-visit interaction. The Restricted Maximum Likelihood Estimation (REML) procedure will be employed using an unstructured covariance matrix. Dose will be treated as a continuous variable, and the control treatment will not be included in this analysis. The p-value from the test of the null hypothesis that the coefficient for the interaction between SB623 dose and the indicator variable for the Week 24 visit equals zero will be presented.

The primary efficacy endpoint will also be analyzed using an analysis of covariance model with the following terms: treatment, the presence of prior (i.e., at baseline) antibodies to donor cell HLA antigens, the interaction between treatment and the presence of prior antibodies to donor cell HLA antigens, the baseline FMMS score, and the GOS-E score at screening to test the null hypothesis that the coefficient of the interaction term equals 0.

The relationship between anti-HLA antibodies and the primary efficacy endpoint will be examined. Descriptive statistics for the primary efficacy endpoint will be presented by treatment group and whether or not the subject experienced an increase of antibodies to donor HLA antigens from baseline to Week 24. A normal approximation test will be used to test the null hypothesis that the differences in means between the pooled SB623 group and the control group are equal for subjects with an increase of antibodies to donor HLA antigens from baseline to Week 24 and those without an increase. Analogous analyses will be performed for whether or not a subject experienced the formation of antibodies post treatment to Week 24 (for subjects with no antibodies at baseline).

The primary efficacy endpoint will be summarized using descriptive statistics for the following subgroups of interest:

- Age at Informed Consent (18-<50 years of age, 50-75 years of age)
- Gender
- GOS-E score at screening (3, 4, 5, or 6)
- Baseline FMMS score (0-50, 51-100)
- Lot (SB623 doses only)
- Percentage cell viability (≤ sample median value, > sample median value)

10.2 Secondary Efficacy Endpoints

The change from baseline in the Disability Rating Scale (DRS) score at Week 24 among all patients, the change from baseline in the Action Research Arm Test (ARAT) total score at Week 24 among upper extremity deficit patients, the change from baseline in Gait Velocity at Week 24 among lower extremity deficit patients, and the change from baseline in the two NeuroQOL subdomain T scores (Upper Extremity Function (Fine Motor ADL) and Lower Extremity Function (Mobility)) at Week 24 among upper and lower extremity deficit patients, respectively, will each be analyzed in a manner analogous to that for the primary efficacy endpoint.

In addition, each of these secondary efficacy endpoints will be analyzed to examine dose response. Analogous statistical methodologies to those used for evaluating dose response for the primary efficacy endpoint will be used for these endpoints.

The proportions 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 (from Baseline) - Subject at Week 24 and on the Global Rating of Perceived Change (from Baseline) - Clinician at Week 24 will be compared to the corresponding proportions of sham surgery control subjects using a logistic regression model with a term for treatment (SB623 or sham surgery) and the baseline Fugl-Meyer Motor Scale score and the GOS-E score at screening as continuous covariates. The endpoints for these analyses are dichotomized variables based on the Global Rating of Perceived Change score (≥6 vs. <6). In addition, both of these secondary efficacy endpoints will be analyzed to examine dose response using a logistic regression model with SB623 dose, the baseline Fugl-Meyer Motor Scale score, and the GOS-E score at screening as continuous covariates in the model. The control treatment will not be included in this analysis.

The secondary efficacy endpoints will be summarized using descriptive statistics or frequencies and percentages for all of the same subgroups of interest as for the primary efficacy endpoint except lot and percentage cell viability.

10.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are as follows:

1. Change from baseline in Fugl-Meyer Motor Scale (FMMS) score at Week 24 among patients with both upper and lower extremity deficits
2. Change from baseline in Fugl-Meyer Motor upper-extremity subscale (UE-FM) score at Week 24 among upper extremity deficit patients
3. Change from baseline in Fugl-Meyer Motor lower-extremity subscale (LE-FM) score at

Week 24 among lower extremity deficit patients

4. Improvement by ⩾6 points at Week 24 from Baseline in UE-FM score among upper extremity deficit patients
5. Improvement by ⩾3 points at Week 24 from Baseline in LE-FM score among lower extremity deficit patients
6. Improvement from Baseline by ⩾10 points at Week 24 in Fugl-Meyer Motor Scale (FMMS) score among all patients
7. Improvement from Baseline by ⩾6 points at Week 24 in Action Research Arm Test (ARAT) score among upper extremity deficit patients
8. Improvement from Baseline 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 in Gait Velocity on standard 10 m walk among lower extremity deficit patients
9. Pre- and post-contrast standard T1 and T2 weighted, dual echo, and FLAIR-MRI among all patients
10. Perfusion MRI among all patients
11. Diffusion tensor imaging (DTI) with tractography among all patients
12. Lower limb motion as measured by leg activity monitor among lower extremity deficit patients (applicable for US and Japan only)
13. Outcome analysis among all patients based on genotyping of polymorphisms at 3 specific loci:
    - HLA – degree of donor/recipient mismatch
    - BDNF Val66Met mutation present (yes/no)
    - ApoE (i.e., homo and heterozygosity for ApoE2, ApoE3, ApoE4 alleles)

The first three exploratory efficacy endpoints will each be analyzed in a manner analogous to that for the primary efficacy endpoint. In addition, each of these exploratory efficacy endpoints will be analyzed to examine dose response. Analogous statistical methodologies to those used for evaluating dose response for the primary efficacy endpoint will be used for these endpoints.

The fourth, fifth, sixth, seventh, and eighth exploratory efficacy endpoints will be summarized using frequencies and percentages and will be analyzed using a logistic regression model with a term for treatment (SB623 or sham surgery) and the baseline value of the endpoint and the GOS-E score at screening as continuous covariates.

The analyses of the last five exploratory efficacy endpoints will be addressed in separate documents.

10.4 Other Efficacy Analyses

The Fugl-Meyer Motor Scale 33-item upper-extremity subscale (UE-FM) score, the 17-item lower-extremity subscale (LE-FM) score, and the FMMS total score will be summarized by visit using descriptive statistics.

The DRS total score and the eight areas of functioning (eye opening, communication ability, motor response, feeding, toileting, grooming, level of functioning, and employability) will be summarized by visit using descriptive statistics.

The ARAT total score, gait velocity (i.e., 10 meter walk time), the two NeuroQOL subdomain T scores (Upper Extremity Function and Lower Extremity Function), and the Global Rating of

Perceived Change (from Baseline) by both Subject and Clinician will each be summarized by visit using descriptive statistics.

Graphs will be presented summarizing the mean value over time by treatment group (pooled SB623 and control) for the following variables: change from baseline in FMMS total score, change from baseline in DRS total score, change from baseline in ARAT total score, changes from baseline in the two NeuroQOL subdomain T scores, change from baseline in gait velocity, change from baseline in the UE-FM score, change from baseline in the LE-FM score, and the Global Rating of Perceived Change (from Baseline) by both Subject and Clinician. The graphs will plot the mean changes (±standard error) over time. The graphs will also present the p-value at each post-baseline timepoint from a two-sample t-test testing the null hypothesis that the true mean change is equal for the two treatments. Similar graphs will be presented by SB623 dose group, but no p-values will be presented.

In order to investigate the magnitude of effect that might be indicative of clinical meaningfulness, Receiver Operating Characteristic (ROC) curves based on responder status will be plotted for the change from Baseline to Week 24 in the following endpoints: FMMS score among all patients, UE-FM score among upper extremity deficit patients, LE-FM score among lower extremity deficit patients (for both methods of imputing missing baseline values for the previous endpoints), ARAT total score among upper extremity deficit patients, gait velocity among lower extremity deficit patients, and the two NeuroQOL subdomain T scores (Upper Extremity Function and Lower Extremity Function) among upper extremity deficit and lower extremity deficit patients, respectively. These ROC curves will be based on the following definition of a responder. A subject will be considered a responder if the subject's Global Rating of Perceived Change from Baseline at Week 24 is ≥ 6. Separate analyses will be done for GRPC-S and GRPC-C. For each of the GRPC versions (GRPC-S and GRPC-C), a table will be produced summarizing the area under the ROC curve (AUC) for each endpoint. The purpose of the ROC curve analyses is to see how predictive each of the endpoints are of the clinical benefit as perceived by the subject and the clinician.

To further investigate clinical meaningfulness, the primary and secondary efficacy endpoints, except the global ratings endpoints, will be summarized using descriptive statistics for the following groups:

- Global Rating of Perceived Change from Baseline at Week 24 - Subject ($\leq 5, \geq 6$)
- Global Rating of Perceived Change from Baseline at Week 24 - Clinician ($\leq 5, \geq 6$)

Graphs of the sample cumulative distribution functions (CDFs) will be produced by treatment (pooled SB623 and Control) for the change from baseline to Week 24 for each of the endpoints listed in the paragraph above discussing ROC curves. These graphs will show the probability of being x or better with 'better' values being to the right on the x-axis, so that for endpoints for which larger values are better (all of the endpoints except gait velocity), the graph will be of 1 - CDF, i.e., $P(X \geq x)$, rather than the CDF. These figures will allow one to compare response rates between treatments for all possible cut-off values for defining response. The Kolmogorov-Smirnov Test will be used to test the null hypothesis that the true CDFs are equal for the two treatments.

The change from baseline in Gait Velocity (10 meter walk time in seconds) to each post-baseline visit among lower extremity deficit patients will also be analyzed using the Wilcoxon rank sum

test to test the null hypothesis that the true mean changes are equal for the two treatments. In addition, for each treatment group, a shift table of frequencies and percentages will be presented summarizing changes in walk time status (< 300 seconds vs. ≥ 300 seconds) from Baseline to each post-baseline visit. McNemar's Test will be used to test the null hypothesis that the true probability of a walk time < 300 seconds is equal at Baseline and the post-baseline visit. For these analyses, for walk times recorded with a value of '999', a blinded review will be performed of the reason the test was not performed. If the subject could not take the test because they were not mobile, they will be assigned a walk time of 300 seconds. If the reason the test was not performed was not related to the subject's ambulatory status, the walk time will be considered missing and the subject will be excluded from the analysis.

12.0 SAFETY ANALYSES

12.1 Adverse Events

All safety analyses will be performed on the safety population.

The summary of AEs will be limited to treatment emergent AEs, 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.

The number and percentage of subjects with at least one adverse event, at least one serious adverse event (SAE), and at least one adverse event that led to discontinuation from the study will be presented. The number and percentage of subjects having an adverse event in each System Organ Class (SOC) and having each individual type of adverse event (Preferred Term) will be presented. Fisher's Exact Test will be used to test for differences between treatments (pooled SB623 vs. sham surgery) in the proportion of subjects experiencing AEs in each SOC. This analysis will also be performed for SAEs, except that no statistical testing will be performed. Adverse events will also be summarized at the event level by SOC/Preferred Term and severity, by SOC/Preferred Term and relationship to study product, by SOC/Preferred Term and relationship to surgery, and by SOC/Preferred Term and action taken.

12.2 Laboratory Tests

Descriptive statistics will be presented by visit for the actual values and the changes from baseline for each quantitative laboratory test (hematology, serum chemistry, and INR) . The difference between treatment groups (pooled SB623 - sham surgery) in the mean change from baseline will also be presented. For each laboratory test, 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 (pooled SB623 vs. sham surgery). Shift tables will summarize changes in status (normal, abnormal) from baseline to each post-baseline time point for each laboratory test. Abnormal lab values will be flagged in the data listings.

12.3 Vital Signs

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 (pooled SB623 - sham surgery) in the mean change from baseline will also be presented. For each vital sign, 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 (pooled SB623 vs. sham surgery). Abnormal vital sign values will be flagged in the data listings. The values in Table 4 are considered vital sign abnormalities.

Table 4. Abnormal Vital Sign Values

Parameter	Abnormal Value
Fever	> 38.4°C
Tachycardia	>115 beats/minute
Bradycardia	< 50 beats/minute
Systolic Blood Pressure	> 150 mmHg
Diastolic Blood Pressure	> 95 mmHg
Hypotension (systolic)	< 85 mmHg
Respiratory Rate	> 20 breaths/minute

12.4 Other Analyses

Medications will be coded using the World Health Organization Drug Dictionary. The number and percentage of subjects taking each type of concomitant medication will be summarized based on the World Health Organization Anatomical Therapeutic Chemical (WHO ATC) Level 4 Class code and generic name.

The number and percentage of subjects with any antibodies to donor HLA antigens and the number and percentage of subjects with an increase in antibody level from baseline will be presented by visit.

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Appendix A: TABLE SHELLS

Appendix B: LISTING SHELLS

Appendix B: FIGURE SHELLS

ADDENDUM TO STATISTICAL ANALYSIS PLAN

Protocol # TBI-01

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)

April 23, 2019

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Sponsor: SanBio, Incorporated

Study Number: TBI-01

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)

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List of Abbreviations

FMMS	Fugl-Meyer Motor Scale
GOS-E	Glasgow Outcome Scale - Extended
MI	Motricity Index
mITT	Modified Intent-to-Treat
MMRM	Mixed Model Repeated Measures
SAS	Statistical Analysis System
TBI	Traumatic Brain Injury

1.0 INTRODUCTION

The purpose of this addendum to the Statistical Analysis Plan for the TBI-01 main study is to (1) provide the justification for imputation of the baseline FMMS score for one patient and (2) to document that the CSR will include additional reporting due to post-hoc analyses.

2.0 JUSTIFICATION FOR IMPUTATION OF THE BASELINE FMMS SCORE FOR ONE PATIENT

For one subject in the mITT population, the baseline FMMS evaluation was performed on the incorrect side. The baseline FMMS score is required in order to calculate change from baseline in the FMMS score at Week 24, the primary study endpoint. There is no data handling convention specified for this situation in the Statistical Analysis Plan. As a post-hoc solution, the baseline value for this subject was imputed as defined below.

The initial step in the imputation was to identify baseline variables that measure the severity of TBI. The variables selected were the Motricity Index (MI) scores (upper and lower) and the baseline Glasgow Outcome Scale - Extended (GOS-E) score. The MI is used to measure strength in the upper and lower extremities after stroke, with the upper and lower scores evaluated on the affected side. The GOS-E score measures the level of disability. For subjects in the mITT population with non-missing baseline FMMS scores, the relationship between these variables and the baseline FMMS score was estimated by performing a linear regression (SAS PROC GLM), with the baseline FMMS score as the dependent variable and the MI and GOS-E scores as independent variables. The parameter estimates obtained from the linear regression were then applied to the subject missing a baseline FMMS evaluation in order to impute a baseline FMMS value. This imputed value was used in the analysis.

A sensitivity analysis on this result was then performed by removing the imputed baseline FMMS value from the primary endpoint analysis. By removing this imputed value, this subject was excluded from the sensitivity analysis.

Since the baseline FMMS evaluation on the correct side was missing, the choice was either to impute the missing value or to exclude the subject from this analysis. As the intent of analyses based on the mITT population is to include all randomized subjects who completed the surgical procedure, the primary analysis was based on imputing this value, but, as described above, a sensitivity analysis was performed with this subject excluded.

3.0 EXPANDED STUDY REPORTING FOR POST-HOC ANALYSES

Some post-hoc analyses were added after unblinding of the results of the interim analysis. The tables and figures presenting the results of these post-hoc analyses will be included in the CSR: these analyses will be numbered as 12.x.x.

Appendix B:

TBI-01 SUPPLEMENT FOR JAPANESE SUBMISSION

STATISTICAL ANALYSIS PLAN: SUPPLEMENT FOR JAPANESE SUBMISSION

Protocol # TBI-01

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)

October 1, 2018

Version 1.0

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Signature Page for Statistical Analysis Plan: Supplement for Japanese Submission

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Study Number:	TBI-01
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)
Date of Plan:	October 1, 2018
Version:	1.0

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Table of Contents

List of Tables

List of Abbreviations

ADL	Activities of Daily Living
AE	Adverse Event
ARAT	Action Research Arm Test
BMI	Body Mass Index
DRS	Disability Rating Scale
FMMS	Fugl-Meyer Motor Scale
GOS-E	Glasgow Outcome Scale - Extended
ITT	Intent-to-Treat
LE	Lower Extremity
LOCF	Last-Observation-Carried-Forward
LSM	Least-Squares Mean
mITT	Modified Intent-to-Treat
MMRM	Mixed Model Repeated Measures
MRI	Magnetic Resonance Imaging
REML	Restricted Maximum Likelihood Estimation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	System Organ Class
TBI	Traumatic Brain Injury
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
UE	Upper Extremity

1.0 INTRODUCTION

The purpose of this Supplement for Japanese Submission to the main Statistical Analysis Plan (SAP) for the TBI-01 study is to describe the additional analysis and tables to be included in the submission to the Japanese regulatory authorities. That submission will also include all of the analyses, tables, and listings described in the main SAP. These additional analyses will descriptively characterize results for Japanese sites and rest of the world (United States and Ukraine) sites so as to be able to compare the results for the two groups of sites. Listings will be done only for the whole study population as specified in the main SAP. The Japanese submission will include all of the analyses and table from the main SAP, the Head MRI SAP, the Genotyping SAP, the Antibody SAP, and the Actigraphy SAP. Separate analyses for Japanese subjects will not be performed, except as shown herein.

2.0 EFFICACY AND SAFETY ENDPOINTS

For the mITT Population (see Section 4.2), 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.

2.1 Primary Efficacy Endpoint

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

2.2 Secondary Efficacy Endpoints

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 (the affected side will be analyzed)
- Change from baseline in Gait Velocity at Week 24 among lower extremity deficit patients (the better of the two trials at the visit will be used for analysis)
- Change from baseline at Week 24 in T scores of NeuroQOL sub-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

3.0 STATISTICAL CONSIDERATIONS

The statistical analysis of the data obtained from this study will be performed using SAS® version 9.4 or higher.

The data collected in this study will be documented using summary tables. Continuous variables will be summarized using descriptive statistics, specifically the number of observations, mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized by frequencies and percentages. For the most part results will be presented for the four treatment

groups separately and the three SB623 dose groups pooled. All results will be presented separately for Japanese sites and Rest of the World sites.

4.0 ANALYSIS POPULATIONS

4.1 Modified Intent-to-Treat Population

The Intent-to-Treat (ITT) population will include all randomized patients. All efficacy analyses will be conducted on the 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.

4.2 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.

5.0 SUBJECT DISPOSITION

The numbers and percentages (based upon the ITT Population) of patients in the ITT Population, in the mITT Population, in the Safety Population, who completed the study, and who discontinued from the study before completion will be presented. For subjects who discontinued from the study before completion, the primary reason for early termination will be summarized using frequencies and percentages.

6.0 DEMOGRAPHICS

Subject demographics collected at the screening visit will be summarized using descriptive statistics for continuous variables (age at informed consent) and frequencies and percentages for categorical variables (sex, race, and ethnicity).

7.0 EFFICACY ANALYSES

7.1 Primary Efficacy Endpoint

The primary analysis will be a comparison of the least-squares mean (LSM) change from baseline in the Fugl-Meyer Motor Scale score of SB623 treated subjects (pooling all SB623 doses) to sham surgery control subjects at Week 24. A mixed model repeated measures (MMRM) analysis will be performed with terms for treatment (SB623 or sham surgery), visit, the treatment-by-visit interaction, the baseline Fugl-Meyer Motor Scale score, the baseline Fugl-Meyer Motor Scale score-by-visit interaction, the GOS-E score at screening, and the GOS-E score at screening-by-visit interaction. The Restricted Maximum Likelihood Estimation (REML) procedure will be employed using an unstructured covariance matrix. The LSM and standard error will be presented for the two treatments, together with a 95% confidence interval for the LSM. The difference in LSMs between treatments and corresponding 95% confidence interval will also be presented.

In addition, the primary efficacy endpoint, the change from baseline in the FMMS score at Week 24, will be analyzed to examine dose response. As for the primary analysis, a mixed model repeated

measures (MMRM) analysis will be performed. The model will include terms for visit, the interaction between SB623 dose and an indicator variable for the Week 4 visit, the interaction between SB623 dose and an indicator variable for the Week 12 visit, the interaction between SB623 dose and an indicator variable for the Week 24 visit, the baseline Fugl-Meyer Motor Scale score, the baseline Fugl-Meyer Motor Scale score-by-visit interaction, the GOS-E score at screening, and the GOS-E score at screening-by-visit interaction. The Restricted Maximum Likelihood Estimation (REML) procedure will be employed using an unstructured covariance matrix. Dose will be treated as a continuous variable, and the control treatment will not be included in this analysis. The p-value from the test of the null hypothesis that the coefficient for the interaction between SB623 dose and the indicator variable for the Week 24 visit equals zero will be presented.

For FMMS score, the following imputation rules will be followed for missing data:

a) impute missing individual items at post-baseline visits using the Last-Observation-Carried-forward (LOCF) method.
b) impute missing individual items at baseline in the following two ways (i. imputed with a score of 0; ii. imputed with the first observed post-baseline value).

7.2 Secondary Efficacy Endpoints

The change from baseline in the Disability Rating Scale (DRS) score at Week 24 among all patients, the change from baseline in the Action Research Arm Test (ARAT) total score at Week 24 among upper extremity deficit patients, the change from baseline in Gait Velocity at Week 24 among lower extremity deficit patients, and the change from baseline at Week 24 in the two NeuroQOL subdomain T scores (Upper Extremity Function (Fine Motor ADL) and Lower Extremity Function (Mobility)) among upper extremity deficit patients and lower extremity deficit patients, respectively, will each be analyzed in a manner analogous to that for the primary efficacy endpoint.

The proportions 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 (from Baseline) - Subject at Week 24 and on the Global Rating of Perceived Change (from Baseline) - Clinician at Week 24 will be compared to the corresponding proportions of sham surgery control subjects using a logistic regression model with a term for treatment (SB623 or sham surgery) and the baseline Fugl-Meyer Motor Scale score and the GOS-E score at screening as continuous covariates. The endpoints for these analyses are dichotomized variables based on the Global Rating of Perceived Change score ($\geq$6 vs. <6).

8.0 SAFETY ANALYSES

The safety analyses will be performed on the safety population.

The summary of AEs will be limited to treatment emergent AEs, 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.

The number and percentage of subjects with at least one adverse event, at least one serious adverse event (SAE), and at least one adverse event that led to discontinuation from the study will be presented. The number and percentage of subjects having an adverse event in each System Organ Class (SOC) and having each individual type of adverse event (Preferred Term) will be presented. This analysis will also be performed for serious adverse events (SAEs). Adverse events will also be summarized at the event level by SOC/Preferred Term and relationship to study product.

Appendix A: TABLE SHELLS

Appendix C:

TBI-01 STATISTICAL ANALYSIS PLAN FOR GENOTYPING VARIABLES

STATISTICAL ANALYSIS PLAN
FOR GENOTYPING VARIABLES

Protocol # TBI-01

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)

October 1, 2018

Version 1.0

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Signature Page for TBI-01 Genotyping Statistical Analysis Plan

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Table of Contents

List of Tables

List of Listings

List of Figures

List of Abbreviations

BDNF	Brain-Derived Neurotrophic Factor
DSMB	Data and Safety Monitoring Board
FMMS	Fugl-Meyer Motor Scale
GOS-E	Glasgow Outcome Scale - Extended
HLA	Human Leukocyte Antigen
IND	Investigational New Drug
ITT	Intent-to-Treat
IXRS	Interactive Web/Voice Response System
LOCF	Last-Observation-Carried-Forward
LSM	Least-Squares Mean
mITT	Modified Intent-to-Treat
OR	Operating Room
PP	Per Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TBI	Traumatic Brain Injury

1.0 INTRODUCTION

This document details the analysis plan for the analyses involving genotyping variables for the study entitled “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)". It describes the proposed efficacy and safety analyses, including planned summary tables, by-subject data listings, and figures. This document is a supplement to the main statistical analysis plan (SAP).

2.0 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.

The objectives of the genotyping statistical analyses are to evaluate the efficacy of intracranial administration of SB623 cells with respect to genotyping variables and to evaluate the effect of intracranial administration of SB623 cells on the primary efficacy endpoint, the change from baseline in the Fugl-Meyer Motor Scale score at Week 24, stratified by the values for various genotyping variables.

3.0 STUDY DESIGN

3.1 Overview

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., United States), Eastern Europe (i.e., Russia and Ukraine), and Asia Pacific (i.e., Japan).

Table 1 in the main SAP lists the procedures to be followed throughout the course of the study. Blood for genotyping will be collected at Baseline.

3.2 Method of Assigning Subjects to Treatment

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 million, 5 million, or 10 million SB623 cells. Randomization will be performed via an interactive web/voice response system (IXRS). 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.

3.3 Blinding

This is a double-blind study. The blind will be maintained by strict role definition and procedures as described in the protocol.

3.4 Changes to the Protocol-Specified Analyses

No changes were made to the protocol-specified analyses.

4.0 EFFICACY AND SAFETY ENDPOINTS IN THIS STATISTICAL ANALYSIS PLAN

4.1 Primary Efficacy Endpoint

The primary efficacy endpoint in the study is the change from baseline in the Fugl-Meyer Motor Scale (FMMS) score at Week 24 among all patients.

4.2 Safety Endpoints

The safety endpoints of interest in this SAP are the presence of serious adverse events (SAEs) and the number of SAEs per patient.

5.0 STATISTICAL CONSIDERATIONS

5.1 General Methodology

The statistical analysis of the data will be performed using SAS® version 9.4 or higher. All statistical tests will be performed at the 0.05 significance level.

Continuous variables will be summarized using descriptive statistics, specifically the number of observations, mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized by frequencies and percentages. For the most part results will be presented for the four treatment groups separately and the three SB623 dose groups pooled. The three SB623 dose groups will be pooled for all statistical tests comparing SB623 to sham surgery, except where noted otherwise (e.g., dose response analyses).

Data listings will be sorted by treatment group and subject ID. All date fields will be presented in a format of ddmmmyyyy (i.e., 01Jan2018) in the listings.

5.2 Adjustments for Covariates

The primary efficacy endpoint, the change from baseline in the Fugl-Meyer Motor Scale (FMMS) score at Week 24, will be analyzed using an analysis of covariance (ANCOVA) model with adjustment for the baseline FMMS score as a continuous covariate.

5.3 Handling of Dropouts and Missing Data

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

For FMMS score, the following imputation rules will be followed for missing data:

(a) Impute missing individual items at post-baseline visits using the Last-Observation-Carried-Forward (LOCF) method.
(b) Impute missing individual items at baseline in the following two ways (i. imputed with a score of 0; ii. imputed with the first observed post-baseline value).

If there are no missing individual items for FMMS score at baseline, then the FMMS results will be shown only once, rather than once for each case specified in (b) above.

5.4 Multicenter Study

Approximately 52 subjects will be randomized into the study at approximately thirty (30) sites in North America (i.e., United States), Eastern Europe (i.e., Russia and Ukraine), and Asia Pacific (i.e., Japan). A maximum of 12 subjects will be enrolled at each Assessment site, and a maximum of 16 subjects will be enrolled or treated at each Surgery or Comprehensive site, respectively.

5.5 Multiple Comparisons / Multiplicity

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

5.6 Examination of Subgroups

The primary analyses of the primary efficacy endpoint will be performed on the following genotype subgroups of interest, which are determined once, at Baseline, with a blood test:

1. HLA typing

2. Presence of BDNF (Brain derived neurotrophic factor) mutation
3. ApoE locus

5.6.1 HLA Genotype

HLA typing compares donor to recipient at each of two alleles for each of the following loci:

a. HLA-A (0 mismatch, 1 mismatch, or 2 mismatches)
b. HLA-B (0 mismatch, 1 mismatch, or 2 mismatches)
c. HLA-C (0 mismatch, 1 mismatch, or 2 mismatches)
d. HLA-DRB1 (0 mismatch, 1 mismatch, or 2 mismatches)
e. HLA-DQB1 (0 mismatch, 1 mismatch, or 2 mismatches)

These results generate the following 3 HLA subgroup categories (by adding up the number of mismatches at each locus), which will be used for the subgroup analyses:

- High degree of mismatch (8-10 mismatches)
- Moderate degree of mismatch (4-7 mismatches)
- Low degree of mismatch (0-3 mismatches)

5.6.2 Presence of BDNF Mutation

For this variable, there are four possible genotype groups.

BDNF Group	Genotype
A	Val/Val
B	Val/Met
C	Met/Met
D	Other

The subgroup analyses will be performed for the following subgroup categories, which have been dichotomized according to whether the subject has at least one Met allele:

BDNF Subgroup	BDNF Groups
No Met alleles	A, D
At least one Met allele	B, C

5.6.3 ApoE Genotype

For this variable, the groups are as follows:

Apo Group	ApoE2	ApoE3	ApoE4	Description
A	0	0	2	Homozygous ApoE4
B	0	1	1	Heterozygous ApoE4
C	1	0	1	Heterozygous ApoE4
D	0	2	0	Homozygous ApoE3
E	1	1	0	Heterozygous ApoE2
F	2	0	0	Homozygous ApoE2
Other				None of the above

The subgroup analyses will be performed for the following subgroup categories:

Apo Subgroup	Apo Groups
At least one ApoE4 allele	A, B, C
No ApoE4 alleles	D, E, F, Other

6.0 ANALYSIS POPULATIONS

6.1 Modified Intent-to-Treat Population

The Intent-to-Treat (ITT) population will include all randomized patients. All efficacy analyses will be conducted on the 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.

6.2 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.

6.3 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.

7.0 EFFICACY ANALYSES

The primary analyses of the primary efficacy endpoint will be comparisons of the least-squares mean (LSM) change from baseline in the Fugl-Meyer Motor Scale score at Week 24 of SB623 treated subjects (pooling all SB623 doses) to sham surgery control subjects for the genotyping subgroup variables defined in Section 5.6. For each genotyping subgroup variable, the relationship between the subgroup variable and the primary efficacy endpoint will be examined in the following manner. An analysis of covariance (ANCOVA) will be performed with terms for treatment (pooled SB623 or sham surgery), subgroup, the treatment-by-subgroup interaction, and the baseline Fugl-Meyer Motor Scale score. Within each subgroup category, the LSM and its standard error will be presented for the two treatments, together with a 95% confidence interval for the LSM. The difference in LSMs between treatments and the corresponding 95% confidence interval will also be presented, as well as the p-value for the test of the null hypothesis that the LSMs are equal for the two treatments. In order to examine whether the treatment effect differs for different categories of the subgroup variable, an F-test will be used to test the null hypothesis that the coefficient of the interaction term equals 0. Missing observations will not be imputed.

In addition, the primary efficacy endpoint, the change from baseline in the FMMS score at Week 24 among all patients, will be analyzed to examine dose response for the genotyping subgroup variables defined in Section 5.6. As for the primary analysis, an analysis of covariance will be performed. The model will include terms for SB623 dose, subgroup, the SB623 dose-by-subgroup interaction, and the baseline Fugl-Meyer Motor Scale score. Dose will be treated as a continuous variable, and the control treatment will not be included in this analysis. The p-value for the test of the null hypothesis that the coefficient of SB623 dose equals 0 will be presented. In order to examine whether the dose effect differs for different values of the subgroup variable, an F-test will be used to test the null hypothesis that the coefficient of the interaction term equals 0 and the p-value will be presented.

Descriptive statistics for the FMMS score at Week 24 and the corresponding change from baseline will be presented by treatment group (control, pooled SB623, and each SB623 dose) and subgroup category for each genotyping subgroup variable. Tables and graphs will be presented summarizing the mean change from baseline in the FMMS score over time by treatment group (pooled SB623 and control) and subgroup category for each genotyping subgroup variable, and tables will be presented by SB623 dose group and subgroup category for each genotyping subgroup variable. The tables will present descriptive statistics. The graphs will plot the mean changes (±standard error) over time. The graphs will also present the p-value at each post-baseline timepoint from a two-sample t-test testing the null hypothesis that the true mean change is equal for the two treatments.

8.0 SAFETY ANALYSES

The summary of SAEs will be limited to treatment emergent SAEs, which are defined as any serious 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 (control patients, pooled SB623 patients, and each SB623 dose group) and each category of each genotyping subgroup variable, the following results will be presented: number and percentage of subjects with at least one SAE and descriptive statistics for the number of SAEs per patient. For each category of each genotyping subgroup variable, a two-sided Fisher's Exact Test will be used to test for a difference between treatments (pooled SB623 versus control) in the proportion of patients with at least one SAE. For each treatment group, a two-sided Fisher's Exact Test will be used to test for a difference among categories of the subgroup variables in the proportion of patients with at least one SAE.

For each genotyping subgroup variable, a logistic regression analysis of SAE incidence will be performed. The model will include terms for the genotyping subgroup variable, treatment (pooled SB623 or control), and the genotyping subgroup variable by treatment interaction. The p-value for each term in the model will be presented. A statistically significant interaction term would indicate that the effect of treatment on SAE occurrence is different among the categories of the genotyping subgroup variable.

For each genotyping subgroup variable, a dose response analysis of the incidence of SAEs will be performed using a logistic regression model with terms for the genotyping subgroup variable, SB623 dose (as a continuous variable), and the genotyping subgroup variable by SB623 dose interaction. The control group will be excluded from these analyses. The p-value for each term in the model will be presented. A statistically significant interaction term would indicate that the effect of dose on SAE occurrence is different among the categories of the genotyping subgroup variable.

Appendix A: TABLE SHELLS

Appendix B: LISTING SHELLS

Appendix C: FIGURE SHELLS

Appendix D:

TBI-01 STATISTICAL ANALYSIS PLAN FOR ANTIBODY VARIABLES

STATISTICAL ANALYSIS PLAN
FOR ANTIBODY VARIABLES

Protocol # TBI-01

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)

October 5, 2018

Version 1.0

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Sponsor:	SanBio, Incorporated
Study Number:	TBI-01
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)
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Table of Contents

List of Tables

Number	Title
1.9	Mean Change from Baseline in Fugl-Meyer Motor Scale (FMMS) Score among All Patients Stratified by Whether or Not the Patient had Either Pre-Existing Donor-Specific Antibodies or a Significant Increase in Donor-Specific Antibodies at any Post-Baseline Visit (mITT Population)
2	Immunogenicity Endpoints (Safety Population)
3	Shift Tables for Immunogenicity Endpoints (Safety Population)
4	Increase in Donor-Specific Antibodies (Safety Population)
5.1	Pearson Product Moment Correlation Between MFI and SB623 Dose (Safety Population)
5.2	Relationship between Whether or not the Patient had a Significant Increase in Donor-Specific Antibodies at any Post-Baseline Visit and the Degree of HLA Mismatch (mITT Population)
6.1	Serious Treatment Emergent Adverse Events (SAEs) (Safety Population)
6.2	Number of Serious Treatment Emergent Adverse Events (SAEs) per Patient (Safety Population)

List of Listings

List of Figures

Number	Title
3.2.1	Mean Change from Baseline in FMMS Score among All Patients (pooled SB623 vs. Control): Patients with Either Pre-Existing Donor-Specific Antibodies or Significant Increase in Donor-Specific Antibodies at any Post-Baseline Visit (missing individual FMMS items at Baseline imputed with first observed post-baseline value) (mITT Population)
3.2.2	Mean Change from Baseline in FMMS Score among All Patients (pooled SB623 vs. Control): Patients with No Pre-Existing Donor-Specific Antibodies and No Significant Increase in Donor-Specific Antibodies at any Post-Baseline Visit (missing individual FMMS items at Baseline imputed with first observed post-baseline value) (mITT Population)
4.1	Mean Donor Antibody Specific MFI Value by Treatment Group (Pooled SB623 vs. Control): All Patients (Safety Population)
4.2	Mean Donor Antibody Specific MFI Value by SB623 Dose: All Patients (Safety Population)
5.1	Mean Donor Antibody Specific MFI Value by Treatment Group (Pooled SB623 vs. Control): Patients with Pre-Existing Donor-Specific Antibodies (Safety Population)
5.2	Mean Donor Antibody Specific MFI Value by SB623 Dose: Patients with Pre-Existing Donor-Specific Antibodies (Safety Population)
6.1	Mean Donor Antibody Specific MFI Value by Treatment Group (Pooled SB623 vs. Control): Patients with No Pre-Existing Donor-Specific Antibodies (Safety Population)
6.2	Mean Donor Antibody Specific MFI Value by SB623 Dose: Patients with No Pre-Existing Donor-Specific Antibodies (Safety Population)

List of Abbreviations

ANCOVA	Analysis of Covariance
DSMB	Data and Safety Monitoring Board
FMMS	Fugl-Meyer Motor Scale
GOS-E	Glasgow Outcome Scale - Extended
HLA	Human Leukocyte Antigen
IND	Investigational New Drug
ITT	Intent-to-Treat
IXRS	Interactive Web/Voice Response System
LOCF	Last-Observation-Carried-Forward
LSM	Least-Squares Mean
MFI	Mean Fluorescence Intensity
mITT	Modified Intent-to-Treat
OR	Operating Room
PP	Per Protocol
PRA	Panel Reactive Antibody
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TBI	Traumatic Brain Injury

1.0 INTRODUCTION

This document details the analysis plan for the analysis of antibody variables for the study entitled “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)". It describes the proposed efficacy and safety analyses, including planned summary tables, by-subject data listings, and figures. This document is a supplement to the main statistical analysis plan (SAP).

2.0 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.

The objectives of the antibody statistical analyses are to characterize the immunogenicity of SB623 and to examine the effect of the immunogenicity variables on efficacy and safety.

3.0 STUDY DESIGN

3.1 Overview

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., United States), Eastern Europe (i.e., Ukraine), and Asia Pacific (i.e., Japan).

Table 1 in the main SAP lists the procedures to be followed throughout the course of the study. Antibody data will be collected at Baseline, and Days 8, 28, 84, 168, and 336.

3.2 Method of Assigning Subjects to Treatment

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 million, 5 million, or 10 million SB623 cells. Randomization will be performed via an interactive web/voice response system (IXRS). 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.

3.3 Blinding

This is a double-blind study. The blind will be maintained by strict role definition and procedures as described in the protocol.

3.4 Changes to the Protocol-Specified Analyses

No changes were made to the protocol-specified analyses.

4.0 EFFICACY AND SAFETY ENDPOINTS IN THIS STATISTICAL ANALYSIS PLAN

4.1 Primary Efficacy Endpoint

The primary efficacy endpoint in the study is the change from baseline in the Fugl-Meyer Motor Scale (FMMS) score at Week 24 among all patients.

4.2 Immunogenicity Endpoints

The immunogenicity endpoints of interest in this SAP are the antibody variables, which are as follows: flow PRA class I reaction, percent PRA class I, flow PRA class II reaction, percent PRA class II, high resolution anti-HLA antibodies detected (yes or no), MFI value, virtual T cell interpretation, virtual B cell interpretation, and change in donor-specific antibodies relative to previous sample (visit).

4.3 Safety Endpoints

The safety endpoints of interest in this SAP are the presence of serious adverse events (SAEs) and the number of SAEs per patient.

5.0 STATISTICAL CONSIDERATIONS

5.1 General Methodology

The statistical analysis of the data will be performed using SAS® version 9.4 or higher. All statistical tests will be performed at the 0.05 significance level.

The antibody variables will be documented using summary tables and subject data listings. Continuous variables will be summarized using descriptive statistics, specifically the number of observations, mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized by frequencies and percentages. For the most part results will be presented for the four treatment groups separately and the three SB623 dose groups pooled. The three SB623 dose groups will be pooled for all statistical tests comparing SB623 to sham surgery, except where noted otherwise (e.g., dose response analyses).

Data listings will be sorted by treatment group and subject ID. All date fields will be presented in a format of ddmmmyyyy (i.e., 01Jan2018) in the listings.

5.2 Adjustments for Covariates

The primary efficacy endpoint, the change from baseline in the Fugl-Meyer Motor Scale (FMMS) score at Week 24, will be analyzed using an analysis of covariance (ANCOVA) model with adjustment for the baseline FMMS score as a continuous covariate.

5.3 Handling of Dropouts and Missing Data

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

For FMMS score, the following imputation rules will be followed for missing individual item data:

> (a) Impute missing individual items at post-baseline visits using the Last-Observation-Carried-Forward (LOCF) method.
> (b) Impute missing individual items at baseline in the following two ways (i. imputed with a score of 0; ii. imputed with the first observed post-baseline value).

If there are no missing individual items for FMMS score at baseline, then the FMMS results will be shown only once, rather than once for each case specified in (b) above.

5.4 Multicenter Study

Approximately 52 subjects will be randomized into the study at approximately thirty (30) sites in North America (i.e., United States), Eastern Europe (i.e., Ukraine), and Asia Pacific (i.e., Japan). A maximum of 12 subjects will be enrolled at each Assessment site, and a maximum of 16 subjects will be enrolled or treated at each Surgery or Comprehensive site, respectively.

5.5 Multiple Comparisons / Multiplicity

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

5.6 Examination of Subgroups

The primary analyses of the primary efficacy endpoint will be performed on the following antibody subgroups of interest:

- Patients with pre-existing donor-specific antibodies [defined as having any one of the following a) MFI > 1000 for antibodies against donor HLA; b) virtual T cell positive; c) virtual B cell positive] versus no pre-existing donor-specific antibodies.
- Patients with a significant increase in donor-specific antibodies at any post-baseline visit versus no increase or a non-significant increase at all post-baseline visits
- Patients with either pre-existing donor-specific antibodies or a significant increase in donor-specific antibodies at any post-baseline visit versus those with neither.

While the subgroup categories in the first bullet represent true subgroups, being defined at baseline, the subgroup categories in the second and third bullets are not true subgroup categories.

In addition, the HLA mismatch subgroup (further defined in the TBI-01 genotyping SAP) is utilized in an analysis described in Section 8.0. The HLA mismatch subgroups are as follows:

- High degree of mismatch (8-10 mismatch)
- Moderate degree of mismatch (4-7 mismatches)
- Low degree of mismatches (0-3 mismatches)

6.0 ANALYSIS POPULATIONS

6.1 Modified Intent-to-Treat Population

The Intent-to-Treat (ITT) population will include all randomized patients. All efficacy analyses will be conducted on the 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.

6.2 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.

6.3 Safety Population

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

7.0 EFFICACY ANALYSES

The primary analyses of the primary efficacy endpoint will be comparisons of the least-squares mean (LSM) change from baseline in the Fugl-Meyer Motor Scale score at Week 24 of SB623 treated subjects (pooling all SB623 doses) to sham surgery control subjects for the antibody subgroup variables defined in Section 5.6. For each antibody subgroup variable, the relationship between the subgroup variable and the primary efficacy endpoint will be examined in the following manner. An analysis of covariance (ANCOVA) will be performed with terms for treatment (pooled SB623 or sham surgery), subgroup, the treatment-by-subgroup interaction, and the baseline Fugl-Meyer Motor Scale score. Within each subgroup category, the LSM and its standard error will be presented for the two treatments, together with a 95% confidence interval for the LSM. The difference in LSMs between treatments and the corresponding 95% confidence interval will also be presented, as well as the p-value for the test of the null hypothesis that the LSMs are equal for the two treatments. In order to examine whether the treatment effect differs for different categories of the subgroup variable, an F-test will be used to test the null hypothesis that the coefficient of the interaction term equals 0. Missing observations will not be imputed.

In addition, the primary efficacy endpoint, the change from baseline in the FMMS score at Week 24 among all patients, will be analyzed to examine dose response for the antibody subgroup variables defined in Section 5.6. As for the primary analysis, an analysis of covariance will be performed. The model will include terms for SB623 dose, subgroup, the SB623 dose-by-subgroup interaction, and the baseline Fugl-Meyer Motor Scale score. Dose will be treated as a continuous variable, and the control treatment will not be included in this analysis. The p-value for the test of the null hypothesis that the coefficient of SB623 dose equals 0 will be presented. In order to examine whether the dose effect differs for different values of the subgroup variable, an F-test will be used to test the null hypothesis that the coefficient of the interaction term equals 0 and the p-value will be presented.

Descriptive statistics for the FMMS score at Week 24 and the corresponding change from baseline will be presented by treatment group (control, pooled SB623, and each SB623 dose) and subgroup category for each antibody subgroup variable. Tables and graphs will be presented summarizing the mean change from baseline in the FMMS score over time by treatment group (pooled SB623 and control) and subgroup category for each antibody subgroup variable, and tables will be presented by SB623 dose group and subgroup category for each antibody subgroup variable. The tables will present descriptive statistics. The graphs will plot the mean changes (±standard error) over time. The graphs will also present the p-value at each post-baseline timepoint from a two-sample t-test testing the null hypothesis that the true mean change is equal for pooled SB623 and control.

8.0 IMMUNOGENICTY ANALYSES

For each treatment group (control patients, pooled SB623 patients, and each SB623 dose group) and each visit the following results will be presented:

- Number and percentage of patients positive for flow PRA class I
- Descriptive statistics for percentage PRA class I
- Number and percentage of patients positive for flow PRA class II reaction
- Descriptive statistics for percentage PRA class II
- Descriptive statistics for MFI value
- Number and percentage of patients with MFI > 1000
- Number and percentage of patients with virtual T cell positive
- Number and percentage of patients with virtual B cell positive
- Number and percentage of patients with change in donor-specific antibodies in each of the following categories: no increase; increase, not significant; increase, significant. (post-baseline visits only).

Shift tables will be presented showing the number and percentage of patients in each cross-classification category (baseline versus worst post-baseline visit, where positive and yes are worse than negative and no, respectively) for the following variables:

1. Flow PRA class I (positive or negative)
2. Flow PRA class II (positive or negative)
3. MFI > 1000 (yes or no)
4. Virtual T cell interpretation (positive or negative)
5. Virtual B cell interpretation (positive or negative)

The shift tables will be done for each treatment group (control, pooled SB623, and each SB623 dose). For variables 1, 2, 4, and 5, among patients who are negative at baseline, a two-sided Fisher's Exact Test will be used to test for a difference in the proportion of patients who are positive at any post-baseline visit between pooled SB623 and control and among the SB623 dose groups. For variable 3, among patients for whom MFI≤1000 at baseline, a two-sided Fisher's Exact Test will be used to test for a difference in the proportion of patients for whom MFI>1000 at any post-baseline visit between pooled SB623 and control and among the SB623 dose groups.

The number and percentage of patients with an increase in donor-specific antibodies, either significant or not significant, at any post-baseline visit will be presented by treatment group (control patients, pooled SB623 patients, and each SB623 dose group). A two-sided Fisher's Exact Test will be used to test for a difference in proportions for pooled SB623 versus control and among SB623 dose groups. Similar analyses will be done for the number and percentage of patients with an increase in donor-specific antibodies, significant, at any post- baseline visit.

The Pearson product moment correlation between MFI and SB623 dose will be presented by visit for the following groups: all SB623 patients, SB623 patients with no pre-existing donor-specific antibodies, and SB623 patients with pre-existing donor-specific antibodies. For each group of patients, the p-value for a two-sided test based on the t-distribution of the null hypothesis of no correlation will be presented.

Figures will be presented showing the mean donor antibody specific MFI value at each visit among control patients and among the pooled SB623 patients, and also among each SB623 dose group. This will also be done for patients with pre-existing donor-specific antibodies and patients with no pre-existing donor-specific antibodies.

The relationship between whether or not the patient had a significant increase in donor-specific antibodies at any post baseline visit will be analyzed using the Cochran-Mantel-Haenszel Test with stratification by treatment (pooled SB623 and control), testing for a difference in mean degree of HLA mismatch between the significant increase in donor-specific antibodies at any post-baseline visit subgroups. For the analysis a low degree of HLA mismatch will be assigned a value of 1.5, a moderate degree of HLA mismatch will be assigned a value of 5.5, and a high degree of HLA mismatch will be assigned a value of 9. These values are the midpoints of the number of HLA mismatches for the HLA subgroups.

9.0 SAFETY ANALYSES

The summary of AEs will be limited to treatment emergent SAEs, which are defined as any serious adverse event with onset on or after the initiation of treatment or any serious adverse event already present that worsens in intensity following exposure to study treatment.

For each treatment group (control patients, pooled SB623 patients, and each SB623 dose group) and each category of each antibody subgroup variable, the following results will be presented: number and percentage of subjects with at least one SAE and descriptive statistics for the number of SAEs per patient. For each category of each antibody subgroup variable, a two-sided Fisher's Exact Test will be used to test for a difference between treatments (pooled SB623 versus control) in the proportion of patients with at least one SAE. For each treatment group, a two-sided Fisher's Exact Test will also be used to test for a difference between categories of the subgroup variables in the proportion of patients with at least one SAE.

For each antibody subgroup variable, a logistic regression analysis of SAE incidence will be performed. The model will include terms for the antibody subgroup variable, treatment (pooled SB623 or control), and the antibody subgroup variable by treatment interaction. The p-value for each term in the model will be presented. A statistically significant interaction term would indicate that the effect of treatment on SAE occurrence is different between the two categories of the antibody subgroup variable.

For each antibody subgroup variable, a dose response analysis of the incidence of SAEs will be performed using a logistic regression model with terms for the antibody subgroup variable, SB623 dose (as a continuous variable), and the antibody subgroup variable by SB623 dose interaction. The control group will be excluded from these analyses. The p-value for each term in the model will be presented. A statistically significant interaction term would indicate that the effect of dose on SAE occurrence is different between the two categories of the antibody subgroup variable.

Appendix A: TABLE SHELLS

Appendix B: LISTING SHELLS

Appendix C: FIGURE SHELLS

Appendix E:

TBI-01 STATISTICAL ANALYSIS PLAN FOR HEAD MRI VARIABLES

STATISTICAL ANALYSIS PLAN
FOR HEAD MRI VARIABLES

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Signature Page for TBI-01 Head MRI Statistical Analysis Plan

Sponsor:	SanBio, Incorporated
Study Number:	TBI-01
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)
Date of Plan	October 8, 2018
Version	1.0

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Table of Contents

List of Tables

Status (Safety Population)

List of Listings

List of Figures

List of Abbreviations

DSC	Dynamic Susceptibility Contrast
DTI	Diffusion Tensor Imaging
FMMS	Fugl-Meyer Motor Scale
GOS-E	Glasgow Outcome Scale - Extended
ITT	Intent-to-Treat
IXRS	Interactive Web/Voice Response System
LOCF	Last-Observation-Carried-Forward
LSM	Least-Squares Mean
mITT	Modified Intent-to-Treat
MMRM	Mixed Model Repeated Measures
MRI	Magnetic Resonance Imaging
PP	Per Protocol
REML	Restricted Maximum Likelihood Estimation
SAP	Statistical Analysis Plan
TBI	Traumatic Brain Injury

1.0 INTRODUCTION

This document details the analysis plan for the analysis of head magnetic resonance imaging (MRI) variables for the study entitled “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)". It describes the proposed efficacy and safety analyses, including planned summary tables and by-subject data listings. This document is a supplement to the main statistical analysis plan (SAP).

2.0 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.

The primary objective of this study is to evaluate the clinical efficacy of intracranial administration of SB623 cells.

The objectives of the head MRI statistical analyses are to evaluate the efficacy of intracranial administration of SB623 cells with respect to head MRI variables and to evaluate the effect of intracranial administration of SB623 cells on the primary efficacy endpoint, the change from baseline in the Fugl-Meyer Motor Scale score at Week 24, stratified by the values for various head MRI variables.

3.0 STUDY DESIGN

3.1 Overview

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., United States), Eastern Europe (i.e., Ukraine), and Asia Pacific (i.e., Japan).

Table 1 in the main SAP lists the procedures to be followed throughout the course of the study. Head MRIs will be obtained at Screening, Baseline, and Days 2, 8, 28, 168, and 336. DTI and DSC imaging will be obtained at Baseline, and Days 28, 168, and 336.

3.2 Method of Assigning Subjects to Treatment

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 million, 5 million, or 10 million SB623 cells. Randomization will be performed via an interactive web/voice response system (IXRS). For subjects in the United States 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.

3.3 Blinding

This is a double-blind study. The blind will be maintained by strict role definition and procedures as described in the protocol.

3.4 Changes to the Protocol-Specified Analyses

No changes were made to the protocol-specified analyses.

4.0 EFFICACY AND SAFETY ENDPOINTS IN THIS STATISTICAL ANALYSIS PLAN

4.1 Primary Efficacy Endpoint

The primary efficacy endpoint in the study is the change from baseline in the Fugl-Meyer Motor Scale (FMMS) score at Week 24 among all patients.

4.2 Other Efficacy Endpoints

The other efficacy endpoints of interest in this SAP are the head MRI imaging variables.

4.3 Safety Endpoints

The safety endpoints of interest in this SAP are the presence of new pathologies (e.g., hematomas, tumors, other pathologies).

5.0 STATISTICAL CONSIDERATIONS

5.1 General Methodology

The statistical analysis of the data will be performed using SAS® version 9.4 or higher. All statistical tests will be performed at the 0.05 significance level.

The head MRI variables will be documented using summary tables and subject data listings. Continuous variables will be summarized using descriptive statistics, specifically the number of observations, mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized by frequencies and percentages. For the most part results will be presented for the four treatment groups separately and the three SB623 dose groups pooled. The three SB623 dose groups will be pooled for all statistical tests comparing SB623 to sham surgery, except where noted otherwise (e.g., dose response analyses).

Data listings will be sorted by treatment group and subject ID. All date fields will be presented in a format of ddmmmyyyy (i.e., 01Jan2018) in the listings.

5.2 Adjustments for Covariates

The primary efficacy endpoint, the change from baseline in the Fugl-Meyer Motor Scale (FMMS) score at Week 24, will be analyzed using a mixed model repeated measures (MMRM) analysis with adjustment for the baseline FMMS score and the GOS-E score at screening as continuous covariates.

5.3 Handling of Dropouts and Missing Data

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

For FMMS score, the following imputation rules will be followed for missing data:

a) impute missing individual items at post-baseline visits using the Last-Observation-Carried-forward (LOCF) method.
b) impute missing individual items at baseline in the following two ways (i. imputed with a score of 0; ii. imputed with the first observed post-baseline value).

If there are no missing individual items for FMMS score at baseline, then the FMMS results will be shown only once, rather than once for each case specified in b) above.

5.4 Multicenter Study

Approximately 52 subjects will be randomized into the study at approximately thirty (30) sites in North America (i.e., United States), Eastern Europe (i.e., Ukraine), and Asia Pacific (i.e., Japan). A maximum of 12 subjects will be enrolled at each Assessment site, and a maximum of 16 subjects will be enrolled or treated at each Surgery or Comprehensive site, respectively.

5.5 Multiple Comparisons / Multiplicity

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

5.6 Examination of Subgroups

The primary analyses of the primary efficacy endpoint and the analyses of the head MRI variables will be performed on the following head MRI subgroups of interest:

- Presence of FLAIR lesion at Day 8
- Presence of enhancing lesion at Day 8
- Location of FLAIR lesion at Day 8

For the purposes of this SAP, when a subject has more than one FLAIR lesion, then the location will be based on the largest lesion. It is recognized that these subgroup variables are measured post-treatment, so they may well be affected by the treatment, but there is interest in the relationship between these variables and the primary efficacy endpoint because it may help to explain what is happening biologically.

The dose response analyses of the primary efficacy endpoint and the head MRI variables will be performed for the following head MRI subgroups of interest:

- Presence of FLAIR lesion at Day 8
- Presence of enhancing lesion at Day 8

Pearson-product moment correlations between the change from baseline in each imaging parameter and the primary efficacy endpoint will be calculated for the following baseline subgroups of interest:

- Age at Informed Consent (18-<50 years of age, 50-75 years of age)
- Gender (male, female)
- Time since injury to treatment (time since injury < median time since injury for all subjects, time since injury ≥ median time since injury for all subjects)
- Baseline FMMS score (0-50, 51-100)

6.0 ANALYSIS POPULATIONS

6.1 Modified Intent-to-Treat Population

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

6.2 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.

6.3 Safety Population

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

7.0 EFFICACY ANALYSES

7.1 Primary Efficacy Endpoint

The primary analyses of the primary efficacy endpoint will be comparisons of the least-squares mean (LSM) change from baseline in the Fugl-Meyer Motor Scale score at Week 24 of SB623 treated subjects (pooling all SB623 doses) to sham surgery control subjects for the head MRI subgroups defined in Section 5.6. A mixed model repeated measures (MMRM) analysis will be performed with terms for treatment (SB623 or sham surgery), visit, the treatment-by-visit interaction, the baseline Fugl-Meyer Motor Scale score, the baseline Fugl-Meyer Motor Scale score-by-visit interaction, the GOS-E score at screening, and the GOS-E score at screening-by-visit interaction. The Restricted Maximum Likelihood Estimation (REML) procedure will be employed using an unstructured covariance matrix. The LSM and its standard error will be presented for the two treatments, together with a 95% confidence interval for the LSM. The difference in LSMs between treatments and corresponding 95% confidence interval will also be presented, as well as the p-value for the test of the null hypothesis that the LSMs are equal for the two treatments. For these analyses, subgroups will only be used for the SB623 doses and not for the control treatment, i.e., although the analyses will be by subgroup, the subgroups will only be for the SB623 doses. All control patients will be used for the analyses. Missing observations will not be imputed.

In addition, the primary efficacy endpoint, the change from baseline in the FMMS score at Week 24 among all patients, will be analyzed to examine dose response for the head MRI subgroups defined in Section 5.6. As for the primary analysis, a mixed model repeated measures (MMRM) analysis will be performed. The model will include terms for visit, the interaction between SB623 dose and an indicator variable for the Week 4 visit, the interaction between SB623 dose and an indicator variable for the Week 12 visit, the interaction between SB623 dose and an indicator variable for the Week 24 visit, the baseline Fugl-Meyer Motor Scale score, the baseline Fugl-Meyer Motor Scale score-by-visit interaction, the GOS-E score at screening, and the GOS-E score at screening-by-visit interaction. The Restricted Maximum Likelihood Estimation (REML) procedure will be employed using an unstructured covariance matrix. Dose will be treated as a continuous variable, and the control treatment will not be included in this analysis. The estimated coefficient for the interaction between SB623 dose and the indicator variable for the Week 24 visit and the p-value from the test of the null hypothesis that the true coefficient for this interaction equals zero will be presented. Descriptive statistics for the primary efficacy endpoint will also be presented by dose group for each head MRI subgroup.

The Pearson product moment correlation between the change from baseline in the FMMS score at Week 24 and the change from baseline in each head MRI variable will be presented by visit for each treatment group (2.5 million SB623 cells, 5 million SB623 cells, 10 million SB623 cells, pooled SB623, and control). The p-value from a two-sided test based on the t-distribution of the null hypothesis that the correlation equals 0 will be presented. This will be done overall and for the baseline subgroups specified in Section 5.6.

Graphs will be presented showing the mean value of the primary efficacy endpoint at each visit among control patients and among the pooled SB623 patients. This will also be done for patients with the presence of a FLAIR lesion at Day 8 and for patients without a FLAIR lesion at Day 8, but not for all patients combined. For the control treatment, the graphs will be done for all control

patients. The graphs will plot the mean changes (±standard error) over time. The graphs will also present the p-value at each post-baseline timepoint from a two-sample t-test testing the null hypothesis that the true mean change is equal for the two treatments.

7.2 Other Efficacy Endpoints

For the pooled SB623 versus sham surgery treatment groups, descriptive statistics will be presented by visit for the actual values and the changes from baseline for each head MRI variable. The difference between treatment groups (pooled SB623 - sham surgery) in the mean change from baseline will also be presented. For each head MRI variable, 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 (pooled SB623 vs. sham surgery). Analyses will be performed overall and for the head MRI subgroups specified in Section 5.6.

In addition, each head MRI variable will be analyzed to examine dose response. For each head MRI variable and treatment group (2.5 million SB623 cells, 5 million SB623 cells, 10 million SB623 cells, pooled SB623, and control), the one- sample t-test will be used to test whether the mean change from baseline equals 0 for each post-baseline time point. Linear regression analyses with a term for dose will be used to test the null hypothesis that the coefficient of dose equals 0. Dose will be a continuous variable with the control treatment assigned a value of 0. The p-value from the test of the null hypothesis that the coefficient of dose equals 0 will be presented. Analyses will be performed overall and for the head MRI subgroups specified in Section 5.6.

The numbers and percentages of subjects with FLAIR lesion at Day 8 and with enhancing lesion at Day 8 will be presented by treatment group. Descriptive statistics will be presented for maximum diameter of FLAIR lesion at Day 8, and the x, y, and z dimensions of FLAIR lesion at Day 8. The number and percentage of subjects will be presented for each FLAIR lesion location at Day 8.

The actual values and changes from baseline will be summarized by visit and presence of FLAIR lesion at Day 8 subgroup for the FMMS score using descriptive statistics.

8.0 SAFETY ANALYSES

The numbers and percentages of subjects with any subdural hematomas and any parenchymal hematomas will be presented by treatment and visit (Days 8, 28, 168, and 336) and by treatment across all visits. Dose response analyses of these two variables will be performed using a logistic regression model with a term for dose as a continuous variable, with the control dose excluded from the analyses. For each treatment, the total numbers of subdural hematomas and parenchymal hematomas across all visits will be presented. Subdural hematoma and parenchymal hematoma volume and status will be summarized by visit using counts and percentages.

Appendix A: TABLE SHELLS

Appendix B: LISTING SHELLS

Appendix C: FIGURE SHELLS

Appendix F:

TBI-01 STATISTICAL ANALYSIS PLAN FOR LEG ACTIVITY MONITORING

STATISTICAL ANALYSIS PLAN
FOR LEG ACTIVITY MONITORING

Protocol # TBI-01

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)

October 1, 2018

Version 1.0

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Signature Page for TBI-01 Leg Activity Monitoring Analysis Plan

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Study Number:	TBI-01
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)
Date of Plan:	October 1, 2018
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Table of Contents

List of Tables

Number	Title
4.1.1	Average Time (unit=minutes) of Moderate or Vigorous Activity per Day (affected side) and Change from Baseline (mITT Population)
4.1.2	Average Time (unit=minutes) of Moderate or Vigorous Activity per Day (affected side) and Change from Baseline (Per Protocol Population)
4.1.3	Average Time (unit=minutes) of Moderate or Vigorous Activity per Day (affected side) and Change from Baseline among Lower Extremity Deficit Patients (mITT Population)
4.1.4	Average Time (unit=minutes) of Moderate or Vigorous Activity per Day (affected side) and Change from Baseline among Lower Extremity Deficit Patients (Per Protocol Population)
4.2.1	Average Time (unit=minutes) of Moderate or Vigorous Activity per Day (affected side) and Change from Baseline: Dose Response (mITT Population)
4.2.2	Average Time (unit=minutes) of Moderate or Vigorous Activity per Day (affected side) and Change from Baseline: Dose Response (Per Protocol Population)
4.2.3	Average Time (unit=minutes) of Moderate or Vigorous Activity per Day (affected side) and Change from Baseline among Lower Extremity Deficit Patients: Dose Response (mITT Population)
4.2.4	Average Time (unit=minutes) of Moderate or Vigorous Activity per Day (affected side) and Change from Baseline among Lower Extremity Deficit Patients: Dose Response (Per Protocol Population)

List of Listings

List of Figures

List of Abbreviations

GOS-E	Glasgow Outcome Scale - Extended
ITT	Intent-to-Treat
IXRS	Interactive Web/Voice Response System
LE	Lower Extremity
LOCF	Last-Observation-Carried-Forward
mITT	Modified Intent-to-Treat
PP	Per Protocol
SAP	Statistical Analysis Plan
TBI	Traumatic Brain Injury

1.0 INTRODUCTION

This document details the analysis plan for the analysis of leg activity monitoring variables for the study entitled “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)". It describes the proposed efficacy analyses, including planned summary tables and by-subject data listings. This document is a supplement to the main statistical analysis plan (SAP).

2.0 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.

The objective of the leg activity monitoring analyses is to evaluate the efficacy of intracranial administration of SB623 cells with respect to leg activity monitoring variables.

3.0 STUDY DESIGN

3.1 Overview

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., United States), Eastern Europe (i.e., Ukraine), and Asia Pacific (i.e., Japan).

Table 1 in the main SAP lists the procedures to be followed throughout the course of the study. Activity data will be downloaded at the clinical site and changes from Baseline in activity parameters will be calculated at Days 28, 84, 168, 252, and 336.

3.2 Method of Assigning Subjects to Treatment

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 million, 5 million, or 10 million SB623 cells. Randomization will be performed via an interactive web/voice response system (IXRS). 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.

3.3 Blinding

This is a double-blind study. The blind will be maintained by strict role definition and procedures as described in the protocol.

3.4 Changes to the Protocol-Specified Analyses

No changes were made to the protocol-specified analyses.

4.0 EFFICACY ENDPOINTS IN THIS STATISTICAL ANALYSIS PLAN

The efficacy endpoints of interest in this SAP are variables from the leg activity monitoring.

5.0 STATISTICAL CONSIDERATIONS

5.1 General Methodology

The statistical analysis of the data will be performed using SAS® version 9.4 or higher. All statistical tests will be performed at the 0.05 significance level.

Leg activity monitoring variables will be documented using summary tables, subject data listings, and summary figures. Continuous variables will be summarized using descriptive statistics, specifically the number of observations, mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized by frequencies and percentages. For the most part results will be presented for the four treatment groups separately and the three SB623 dose groups pooled. The three SB623 dose groups will be pooled for all statistical tests comparing SB623 to sham surgery, except where noted otherwise (i.e., dose response analyses).

Data listings will be sorted by treatment group and subject ID. All date fields will be presented in a format of ddmmmyyyy (i.e., 01Jan2018) in the listings.

5.2 Adjustments for Covariates

No adjustments for covariates will be made.

5.3 Handling of Dropouts and Missing Data

Every effort will be made to minimize the number of dropouts and to document reasons for dropping out. The following rules will be followed for missing leg activity monitoring data:

- Missing daily values within a 2-week period will be imputed as the mean of the non-missing daily values for the period.
- If a subject is missing all values for a 2-week post-baseline period and has not discontinued the study, the Last-Observation-Carried-Forward (LOCF) method will be used to impute the value for the 2-week period.

5.4 Multicenter Study

Approximately 52 subjects will be randomized into the study at approximately thirty (30) sites in North America (i.e., United States), Eastern Europe (i.e., Ukraine), and Asia Pacific (i.e., Japan). A maximum of 12 subjects will be enrolled at each Assessment site, and a maximum of 16 subjects will be enrolled or treated at each Surgery or Comprehensive site, respectively.

5.5 Multiple Comparisons / Multiplicity

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

5.6 Examination of Subgroups

The analyses of the leg activity monitoring variables for the affected side will be performed on the following subgroup of interest:

- Lower extremity deficit patients (lower extremity deficit patients are those patients with a Motricity LE Scale score at Screening of 10-78)

6.0 ANALYSIS POPULATIONS

6.1 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.

6.2 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.

7.0 EFFICACY ANALYSES

In this SAP, the following variables from Leg Activity Monitoring will be analyzed.

- Average Daily Total Energy Expenditure (affected side and non-affected side separately)
- Average Daily Activity Counts (affected side and non-affected side separately)
- Average Non-Sedentary Time per Day (affected side)
- Average Time of Moderate or Vigorous Activity per Day (affected side)

For the first two endpoints listed above, the value of the endpoint will be calculated as follows. The mean of each day's value will be calculated for the two-week period prior to Baseline, which will be the baseline value for this endpoint, and for the two-week period prior to each study visit.

Average Non-Sedentary Time per Day: The leg activity monitor can measure the time in minutes within each activity range. Activity range is categorized as sedentary, light, moderate, or vigorous based on energy expenditure. The light, moderate, and vigorous activity ranges are considered non-sedentary. The mean of each day's time within the non-sedentary range will then be obtained for the two-week period prior to Baseline, which will be the baseline value for this endpoint, and for the two-week period prior to each study visit.

Average Time of Moderate or Vigorous Activity per Day: The leg activity monitor can measure the total amount of time in minutes within the moderate or vigorous activity ranges throughout each day. The mean of each day's value will then be calculated for the two-week period prior to Baseline, which will be the baseline value for this endpoint, and for the two-week period prior to each study visit.

For the pooled SB623 and sham surgery treatment groups, descriptive statistics will be presented by visit for the actual values and the changes from baseline for each leg activity monitoring variable. The difference between treatment groups (pooled SB623 - sham surgery) in the mean change from baseline will also be presented. For each leg activity monitoring variable, the one-sample t-test will be used to test whether the mean change from baseline equals 0 for each post-baseline time point for each treatment group. Two-sided, two-sample t-tests will be used to test whether the mean changes from baseline are equal for the two treatments (pooled SB623 vs. sham surgery). Analyses will be performed overall and for the subgroups specified in Section 5.6.

In addition, each leg activity monitoring variable will be analyzed to examine dose response. For each leg activity monitoring variable and SB623 dose group (2.5 million SB623 cells, 5 million SB623 cells, 10 million SB623 cells), a two-sided, one-sample t-test will be used to test whether the mean change from baseline equals 0 for each post-baseline time point. Linear regression analyses with a term for dose will be used to test the null hypothesis that the coefficient of dose equals 0. Dose will be treated as a continuous variable, and the control treatment will not be included in this analysis. The p-value for the test of the null hypothesis that the coefficient of SB623 dose equals 0 will be presented.

Analyses will be performed overall and for the subgroup specified in Section 5.6.

Graphs will be presented summarizing the mean change from baseline in the Average Daily Activity Count (affected side and non-affected side separately) over time by treatment group (pooled SB623 and control) for both the mITT and Per Protocol populations. The graphs will plot

the mean changes (±standard error) over time, as well as the p-value at each timepoint from a two-sided, two-sample t-test testing the null hypothesis that the true mean change is equal for the two treatments.

Appendix A: TABLE SHELLS

Appendix B: LISTING SHELLS

Appendix C: FIGURE SHELLS

ADDENDUM TO STATISTICAL ANALYSIS PLAN

Protocol # TBI-01

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)

April 23, 2019

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Sponsor: SanBio, Incorporated

Study Number: TBI-01

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)

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Table of Contents

List of Abbreviations

FMMS	Fugl-Meyer Motor Scale
GOS-E	Glasgow Outcome Scale - Extended
MI	Motricity Index
mITT	Modified Intent-to-Treat
MMRM	Mixed Model Repeated Measures
SAS	Statistical Analysis System
TBI	Traumatic Brain Injury

1.0 INTRODUCTION

The purpose of this addendum to the Statistical Analysis Plan for the TBI-01 main study is to (1) provide the justification for imputation of the baseline FMMS score for one patient and (2) to document that the CSR will include additional reporting due to post-hoc analyses.

2.0 JUSTIFICATION FOR IMPUTATION OF THE BASELINE FMMS SCORE FOR ONE PATIENT

For one subject in the mITT population, the baseline FMMS evaluation was performed on the incorrect side. The baseline FMMS score is required in order to calculate change from baseline in the FMMS score at Week 24, the primary study endpoint. There is no data handling convention specified for this situation in the Statistical Analysis Plan. As a post-hoc solution, the baseline value for this subject was imputed as defined below.

The initial step in the imputation was to identify baseline variables that measure the severity of TBI. The variables selected were the Motricity Index (MI) scores (upper and lower) and the baseline Glasgow Outcome Scale - Extended (GOS-E) score. The MI is used to measure strength in the upper and lower extremities after stroke, with the upper and lower scores evaluated on the affected side. The GOS-E score measures the level of disability. For subjects in the mITT population with non-missing baseline FMMS scores, the relationship between these variables and the baseline FMMS score was estimated by performing a linear regression (SAS PROC GLM), with the baseline FMMS score as the dependent variable and the MI and GOS-E scores as independent variables. The parameter estimates obtained from the linear regression were then applied to the subject missing a baseline FMMS evaluation in order to impute a baseline FMMS value. This imputed value was used in the analysis.

A sensitivity analysis on this result was then performed by removing the imputed baseline FMMS value from the primary endpoint analysis. By removing this imputed value, this subject was excluded from the sensitivity analysis.

Since the baseline FMMS evaluation on the correct side was missing, the choice was either to impute the missing value or to exclude the subject from this analysis. As the intent of analyses based on the mITT population is to include all randomized subjects who completed the surgical procedure, the primary analysis was based on imputing this value, but, as described above, a sensitivity analysis was performed with this subject excluded.

3.0 EXPANDED STUDY REPORTING FOR POST-HOC ANALYSES

Some post-hoc analyses were added after unblinding of the results of the interim analysis. The tables and figures presenting the results of these post-hoc analyses will be included in the CSR: these analyses will be numbered as 12.x.x.