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Protocol SB-STR01

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

Statistical Analysis Plan

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List of Abbreviations and Definitions

AE	Adverse Event
AFP	Alpha-fetoprotein
ATC	Anatomical Therapeutic Class
CEA	Carcinoembryonic antigen
CI	Confidence Interval
CFB	Change From Baseline
DSMB	Data Safety Monitoring Board
DLT	Dose Limiting Toxicity
ESS	European Stroke Scale
FDG	Fluorodeoxyglucose
IHC	inVentiv Health Clinical
HEENT	Head Ears Eyes Nose Throat
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MRS	Modified Rankin Score
N	Count of Patients
NIHSS	National Institutes of Health Stroke Scale
PBMC	Peripheral Blood Mononuclear Cells
PET	Positron Emission Tomography
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
STC	Standard Toxicity Criteria
TEAE	Treatment-Emergent Adverse Event
WASI	Wechsler Abbreviated Scale of Intelligence
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

1. INTRODUCTION/BACKGROUND

This document describes the statistical methods, data handling procedures, and data presentations to be used in the analysis of data for study SB-STR01. This analysis plan is based on protocol amendment 4.5, dated 22 March 2013.

All statistical analyses and data presentations will be performed by the biostatistics group at inVentiv Health Clinical (IHC) using SAS®, version 9.2 or higher.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE(S)

To evaluate the safety and tolerability of intracranial administration of SB623 cells. Safety will be determined during 2 years post-implant.

2.2 SECONDARY OBJECTIVE(S)

To evaluate clinical and radiographic response to 3 dose levels of intracranial SB623 cell administration. The major efficacy endpoints will be evaluated at 6 months post-implant; measures will also be taken at 1, 2, 3, 4, 9, 12 and 24 months post-implant.

3. STUDY DESIGN

3.1 OVERVIEW

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

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

3.2 STUDY POPULATION

The study population consists of adult patients with hemiparesis from stable ischemic stroke. Stable stroke will be defined as 6-36 mos. post stroke with motor neurological deficit, post-physical therapy, and with no more than ±1 point change in clinical stroke evaluation (using NIHSS) in the 3 weeks prior to study enrollment. The interval of 6-36 months for this patient population is based on a number of studies that have shown that over 90% of ischemic stroke patients are stable by 90 days post-stroke. The upper limit of 36 months was chosen to allow for the possibility of some brain tissue plasticity remaining, while mainly to increase the potential patient population.

3.3 SAMPLE SIZE CALCULATION/JUSTIFICATION

This multi-center study at up to 8 sites uses a sample size of 6 patients per cohort, yielding 18 total evaluable patients at 3 dose levels. Based on the animal safety studies of SB623, no DLT is expected. However, if the true rate of toxicity is 40%, a sample size of 6 patients per cohort would result in a < 5% chance of missing a DLT.

3.4 STUDY ASSESSMENTS

A table of study assessments can be found in Appendix 10.1.

4. ANALYSIS SETS

4.1 EFFICACY POPULATION

Intent-to-Treat (ITT): The intent-to-treat (ITT) population will include all enrolled patients. Enrolled patients are patients who meet all inclusion/exclusion criteria and qualified for the study or who were granted exceptions to selected inclusion/exclusion criteria, meet all other inclusion/exclusion criteria and qualified for the study, including those who were discontinued from the study or withdrawn for any reason. The ITT population will be used in all efficacy analyses.

4.2 SAFETY POPULATION

Safety Population: The safety population will include all enrolled patients who have received treatment with SB623 and who have any post-baseline data. The safety population will be used in all safety analyses.

5. DEFINITIONS AND DERIVED VARIABLES

Age: Age will be calculated as follows:
[Date of Informed Consent – Date of Birth] / 365.25 rounded down to the nearest integer.

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

Concomitant medications: Concomitant medication is defined as any medication, including prescription and over-the-counter drugs taken during the 14 days prior to enrollment or used anytime during the study through 2 years post study treatment administration.

Baseline: Baseline will be defined as the last assessment available prior to first infusion of study treatment.

Change from Baseline (CFB): Change will be defined as a given post-baseline value minus the baseline value.

Dose Limiting Toxicity (DLT): A dose-limiting toxicity will be defined as any grade 3 or 4 event which is at least possibly related to study product or administration procedure.

6. ENDPOINTS AND COVARIATES

6.1 EFFICACY ENDPOINTS

The primary clinical efficacy endpoint for this study is improvement over baseline of total score and motor function total score using the European Stroke Scale (ESS) at 6 months with all SB623 doses pooled.

Secondary clinical endpoints include (all SB623 doses pooled):

- Improvement of total score, motor function total score, and motor function upper and lower extremity score over baseline using the NIHSS at 6 months of the affected side
- Improvement of scalar assessment over baseline using the MRS at 6 months
- Improvement of total score, motor function total score, and motor function upper and lower extremity score over baseline using the Fugl-Meyer scale at 6 months

Exploratory clinical endpoints include (all SB623 doses pooled):

- Improvement of total score and motor function total score over baseline using the ESS at 1, 2, 3, 4, 9, 12, and 24 months

- Improvement of total score, motor function total score, and motor function upper and lower extremity score over baseline using the NIHSS at 1, 2, 3, 4, 9, 12, and 24 months of the affected side
- Improvement of scalar assessment over baseline using the MRS at 1, 2, 3, 4, 9, 12, and 24 months
- Improvement of total score, motor function total score, and motor function upper and lower extremity score over baseline using the Fugl-Meyer scale at 1, 2, 3, 4, 9, 12, and 24 months
- Improvement in cognitive status using a test battery as described in Table 1 at 6, 12 and 24 months

The exploratory radiographic efficacy endpoints for this study is increase in FDG uptake measured by PET at 6, 12 and 24 months and tissue ratio measured by PET at 6, 12, and 24 months with all SB623 doses pooled.

6.1.1 Description of Clinical Assessment Methods

- European Stroke Scale (ESS): The European Stroke Score is the sum of all 14 parameters. A completely normal person will have a score of 100. The European Stroke Motor Function Score is a sum of the selected parameters: Facial movement, Arm in outstretched position, Arm raising, Extension of wrist, Fingers, leg maintained in position, Leg flexing, Dorsiflexion of foot, and Gait. A completely normal person will have a score of 66. The maximally affected person will have a score of 0 for their total score and motor function total score.
- National Institutes of Health Stroke Scale (NIHSS): The NIHSS is a standardized method used to measure the level of impairment caused by a stroke. The scale consists of 11 items which measures several aspects of brain function, including consciousness, vision, sensation, movement, speech, and language. A certain number of points are given for each impairment uncovered during a focused neurological examination. A maximal score of 42 represents the most severe and devastating stroke with 0 = no stroke, 1-4 = minor stroke, 5-15 = moderate stroke, 15-20 = moderate/severe stroke, and 21-42 = severe stroke. The NIHSS Motor Function Total Score will consist of 3 items: Motor Arm, Motor Leg, and Limb Ataxia and a maximal score of 18 represents the most severe for motor function.
- Modified Rankin Scale (MRS): The MRS is a 1-item Likert scale from 0-5 with 0 representing “No symptoms at all” to 5 representing “Severe disability, bedridden, incontinent requiring constant nursing care, and attention”.
- Fugl-Meyer Scale: The Fugl-Meyer Scale is a stroke-specific, performance-based impairment index. It is designed to assess motor functioning, balance, sensation, and joint functioning. The scale is comprised of five domains and there are 155 items in total. Scoring is based on direct observation of performance. Scale items are scored on the basis of ability to complete the item using a 3-point ordinal scale where 0=cannot perform, 1=performs partially, and 2=performs fully. The total possible scale score is 226.

Points are divided among the domains as follows:

- *Motor score:* ranges from 0 (hemiplegia) to 100 points (normal motor performance).
  Divided into 66 points for upper extremity and 34 points for the lower extremity. Total motor scores (out of 100 points) are classified based upon the following impairment severity. Total motor scores of <50 = Severe, 50-84 = Marked, 85-94 = Moderate, and 95-99 = Slight.
- *Sensation:* ranges from 0 to 24 points.
  Divided into 8 points for light touch and 16 points for position sense.
- *Balance:* ranges from 0 to 14 points.
  Divided into 6 points for sitting and 8 points for standing.
- *Joint range of motion:* ranges from 0 to 44 points.
- *Joint pain:* ranges from 0 to 44 points

For purposes of this analysis, the total Fugl-Meyer score, the total of the upper and lower extremity motor score, the total of the upper extremity motor score and the total of the lower extremity motor score will be used. For the motor scores, the total for the upper extremity will be the total of the questions from Sections A-D of the Fugl-Meyer CRF (34 questions with a maximum score of 68 points) and the total for the lower extremity will be the total of the questions from Sections E-G of the Fugl-Meyer CRF (27 questions with a maximum score of 54 points).

- Cognitive Battery: Scoring on the tests within the cognitive battery, as detailed in Table 1, are done by the site based upon source documentation provided by the site. Only total score/time/number of correct items are captured on the CRF and entered into the study database. Complete descriptions of the scales and scoring of each test will be described in detail in the clinical study report.

Table 1 – Cognitive Function Test Battery

Estimated Intelligence
*Wechsler Abbreviated Scale of Intelligence (WASI) 2 Test
Language
Controlled Oral Word Association Category
Vocabulary (WASI)
Attention
Trails A Time
Digit Vigilance Accuracy
Learning and Memory
Rey Auditory Learning Test
Rey Complex Figure – immediate & delayed recall
Logical Memory – WMS-III
Working Memory
Trails B time and errors

Letter-Number Sequencing- WMS-III
Visuospatial/Constructional Ability
Rey Complex Figure Copy
Matrix Reasoning--WASI
Psychomotor Efficiency
Digit Vigilance Time
Trails A Errors
Digit Symbol Substitution Test -WAIS-III
Grooved Pegboard
Executive Function (reasoning, mental manipulation)
Stroop Interference
Controlled Oral Word Association--FAS
Mood State and Quality of Life
Beck Depression Inventory, 2nd Ed.
Beck Anxiety Inventory

* Baseline only
† Administered by other study personnel

6.2 SAFETY ENDPOINTS

The safety and tolerability of SB623 cells will be summarized in terms of the following:

- Adverse events (AEs)
- Dose-Limiting Toxicities (DLTs) grade 3 or higher events related to study product or administration procedure
- AEs related to the surgical procedure
- SB623-related AEs
- Serious Adverse Events (SAEs)
- Adverse changes imaged by head magnetic resonance imaging (MRI) (edema, adverse anatomical changes)
- Clinically significant changes in laboratory tests
- Clinically significant changes in physical exam and vital signs
- Development of SB623 serum antibodies
- Changes in PBMC function
- Changes in plasma cytokines

7. STATISTICAL METHODOLOGY AND ANALYSES

7.1 GENERAL CONSIDERATIONS

Descriptive statistics for continuous variables will include the count of patients (N), mean, standard deviation (SD), median, minimum, maximum and confidence interval (CI, as appropriate); for categorical variables, descriptive statistics will include the number and percentage of patients for each category. Unless otherwise indicated, percentages will be calculated based upon patients with non-missing data as the denominator. When appropriate data will be summarized by dose and visit/time point.

In summary and analysis tables of continuous variables, the minimum and maximum statistics will be presented to the same number of decimal places as the original data. The mean, median, quartiles, and 2-sided 95% confidence interval (CI) will be presented to 1 more decimal place than the original data. The standard deviation and standard error will be presented to 2 more decimal places than the original data.

Analysis of the efficacy endpoints (primary, secondary, and exploratory) will be based on the ITT population defined in Section 4.1. Assessments of tolerability and safety will be based on the safety population defined in Section 4.2.

There are no changes in the protocol-specified analyses.

7.1.1 Hypotheses and Decision Rules

The study is a Phase 1/2A study, with the primary objective of safety and tolerability, and is therefore not powered for multiple efficacy endpoints. All efficacy evaluations are exploratory and no adjustment for multiplicity will be performed. Hypothesis testing of each endpoint will be independently carried out at the 5% (2-sided) significance level.

All statistical analyses will be performed using SAS® v9.2 or higher.

7.1.2 Handling of Missing Values

All analysis will be based on available data. No imputations will be made for missing data unless otherwise specified. Missing baseline measurements may be replaced with the patient's value recorded during the latest visit before study treatment administration, if applicable.

7.1.3 Pooling of Sites

Data will be pooled from up to 8 sites for this analysis. The justification for pooling is made on a clinical basis (Meinert, 1986). The basis for pooling comes from three critical factors: 1) The study sites must implement one common protocol. 2) The sponsor must provide very close monitoring of study site compliance. 3) The study sites must use common data collection procedures.

7.2 PATIENT CHARACTERISTICS

7.2.1 Patient Disposition and Enrollment

Complete accounting of patient participation (from entrance into the study through final visit) in the study will be presented in the summary table for patient disposition. The table will include the following: total completing the study, number of patients who

withdrew, and reasons for early withdrawal. The table will be summarized by cohort and pooled across cohorts. Patient disposition will also be summarized by visit within each cohort.
The number and percentage of enrolled patients enrolled at each site will be summarized by cohort and pooled across cohorts. The number and percentage of patients who are included in each analysis population will also be presented by cohort and pooled across cohorts.

A listing of patient disposition will be provided.

7.2.2 Demographic Characteristics

Patient demographics, such as age, sex, race and ethnicity will be summarized with descriptive statistics.

A listing of patient demographics will be provided.

7.2.3 Protocol Deviations

All instances of failure to comply with the study protocol will be tracked during the study. Prior to database lock the sponsor will decide whether any patients or any individual parameters pertaining to a patient will be excluded from the safety and efficacy evaluations when the protocol deviation is considered to have a negative impact on scientific aspects and interpretation of the study results.

All protocol deviations will be listed.

7.2.4 Treatment Exposure

Using the surgical and implantation procedures as described in Protocol Section 6.0, and preparation and administration as described in Protocol Section 11.4, one burr hole will be made in the skull of the patient in a location that will allow ready access to the infarct region. Cells will be implanted using 3 needle tracks with 5 cell deposits for each track at varying depths. Cell implantation will be standardized as to volume (20 µL/deposit) and rate (10 µL /min), with spacing between each implant of approximately 5-6 mm.

Data that are collected and related to cell administration will be listed.

7.2.5 Concomitant Medications

All concomitant medications including prescription and over-the-counter drugs taken during the 14 days prior to enrollment or used anytime during the study through 2 years post study treatment administration will be documented. Documentation (through month 9 only) will include changes from the prior visit, start and stop dates, dose, and reasons for the medication use. Concomitant medication data will be coded using World Health Organization Drug Dictionary (WHODD) September 2012 (or later). All concomitant medication data will be summarized by anatomical therapeutic class (ATC) and preferred name with ATC.

A listing of all concomitant medications and nondrug therapies will be included.

7.2.6 Medical History

Medical history will include significant medical conditions, diagnosis and/or surgical history occurring prior to informed consent or changes occurring between signing of informed consent and study treatment administration. Medical history events will be classified based on the MedDRA dictionary, version 15.1 (or higher), and summaries will be based on preferred term and system organ class (SOC).

A listing of all medical history will be provided.

7.2.7 Ischemic Stroke History

Ischemic stroke history will include date and cause of stroke, date confirmed if by CT or MRI, and location/size (volume in cc) of the affected brain region or changes occurring between signing of informed consent and study treatment administration.

A listing of ischemic stroke history will be provided.

7.2.8 Signs and Symptom History

Baseline signs and symptoms will include a general survey of impairment at baseline or changes occurring between signing of informed consent and study treatment administration. Categories of impairment include, but are not limited to; difficulty reading, difficulty writing, difficulty speaking, difficulty swallowing, incontinence.

A listing of signs and symptom history will be provided.

7.2.9 12-Lead ECG and Chest X-Ray

A listing of all baseline ECG values will be provided. A listing of baseline chest x-ray results will also be provided.

7.2.10 Occult Malignancy Tests

A listing of all occult malignancy tests (hemoccult, chest x-ray finding, carcinoembryonic antigen (CEA) level, prostate-specific antigen level, CA-125 level, alpha-fetoprotein (AFP) level, and beta-HCG level), test date, and the results will be provided.

7.3 EFFICACY ANALYSES FOR EACH COHORT AND COMBINED COHORTS

7.3.1 Primary Efficacy Analyses

The primary clinical analysis will be a pooled analysis of change from baseline at 6 months for ESS total score and motor function total score, using the ITT population as defined in Section 4.1. The primary radiographic analysis will be a pooled analysis of change from baseline at 6 months in FDG uptake as measured by PET scan, using the ITT population.

Wilcoxon Signed Rank test for change from baseline of each endpoint will be independently assessed using a two-sided significance level of 0.05, without correction for multiplicity.

A listing of ESS scores and FDG-PET parameters, including dates of MRI and CT scans, will be included.

7.3.2 Secondary Efficacy Analyses

The secondary clinical analyses will be pooled analyses of changes from baseline at 6 months for NIHSS total score, motor function total score and motor function upper and lower extremity score; MRS scalar assessment; Fugl-Meyer total score, motor function total score and motor function upper and lower extremity score; and cognitive status using the ITT population.

Wilcoxon Signed Rank tests for change from baseline of each endpoint will be independently assessed using a two-sided significance level of 0.05, without correction for multiplicity.

Listings of NIHSS, MRS, Fugl-Meyer Scores and Cognitive Function Test assessment results will be included.

7.3.3 Exploratory Efficacy Analyses

The exploratory clinical analyses will be pooled analyses of changes from baseline at 1, 2, 3, 4, 9, 12, and 24 months for ESS total score and motor function total score; NIHSS total score, motor function total score and motor function upper and lower extremity score; MRS scalar assessment; and Fugl-Meyer total score, motor function total score and motor function upper and lower extremity score. Pooled analyses of changes from baseline at 12 and 24 months will be conducted for Cognitive Tests and FDG-PET uptake. Exploratory analysis of FDG-PET tissue ratio at 6, 12, and 24 months will also be included. All exploratory analysis will use the ITT population. Inferential tests for change from baseline of each endpoint at each visit will be independently assessed using a two-sided significance level of 0.05.

A mean change from baseline by visit results for the ESS total score; NIHSS total score, motor function total score, and motor function upper and lower extremity score of affected side; MRS scalar assessment; Fugl-Meyer total score, motor function total score, and motor function upper and lower extremity score; and FDG-PET uptake will be graphically presented by individual dose and pooled dose.

7.4 SAFETY ANALYSES FOR EACH COHORT AND COMBINED COHORTS

Incidence of adverse events, dose-limiting toxicities, serious adverse events, clinically significant changes in laboratory data, physical exam, and vital signs, changes in head MRI exams, antibody development, and changes in PBMC function will be analyzed to evaluate the safety of SB623 for all patients in the safety population through 2 years post study treatment administration.

Physical exam and vital sign data, absolute and change from baseline, will be listed by patient by visit. Laboratory data values falling above or below normal range and considered clinically significant will be indicated on the corresponding laboratory listings. Any changes in MRI images at visits post study treatment administration will be indicated in the MRI listing. Presence of antibodies to SB623 (see Section 7.4.6) will be indicated in the antibody listing by patient by visit. PBMC function, the cytokine measurements, will be listed by patient by visit. Descriptive statistics for absolute and change from baseline values will be displayed for each continuous laboratory parameter at each time point.

7.4.1 Adverse Events

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to study treatment administration or any event already present that worsens in either intensity or frequency following exposure to study treatment.

Adverse events will be classified based on the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, version 15.1 (or higher). Analyses will be conducted on preferred term and primary system organ class (SOC). All adverse event data will be listed per patient including severity, relationship to study treatment, and action taken. Event severity is based on the World Health Organization (WHO) standard toxicity criteria (STC).

A Dose-limiting toxicity (DLT) will be defined as any grade 3 or 4 event which is at least possibly related to study product or administration procedure.

The adverse event reporting period for this trial begins upon receiving the dose of study treatment and ends 24 months after the administration of SB623.

The following summaries of AEs will be provided:

- TEAEs by MedDRA SOC and by preferred term
- TEAEs by maximum severity (mild, moderate, severe, life-threatening) by MedDRA SOC and preferred term
- TEAEs by relationship to study treatment by not related (includes unrelated and unlikely related) or related (includes possibly, probably, and definitely related) by MedDRA SOC and preferred term.
- AEs resulting in discontinuation from the study, by MedDRA SOC and preferred term
- SAEs by MedDRA SOC and preferred term
- The following listings of adverse events will be provided (TEAEs will be denoted in each listing):
    - All AEs
    - All Dose-Limiting Toxicities (DLTs)
    - Adverse events resulting in discontinuation from the study
    - Deaths (if any)
    - Serious adverse events
    - AE mappings to MedDRA dictionary terms

7.4.2 Changes in MRI

The CRF collects investigator reported presence or absence of changes in head MRI images at follow-up visits. When changes are reported in MRI images post baseline, details of the event are reported as an AE. The MRI listing includes an indication of presence or absence of changes in MRI images at follow-up visits.

7.4.3 Laboratory Data

All safety laboratory evaluations will be conducted at the laboratories located at or associated with the clinical site. Laboratory values will include hematology, serum chemistry, INR, plasma cytokines, and lipid panels. Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be presented for qualitative laboratory values. Laboratory values will be assessed for change from baseline by visit. All treatment-emergent abnormal chemistry and hematology values meeting toxicity criteria will be summarized by test across study visits. Toxicity criteria are defined in Appendix 10.2.

The absolute and change from baseline results for each laboratory test will be summarized. Patients with missing data for a given time point will not contribute to the tabulations for that time point. Data listings will include all laboratory results by patient by visit. Patients with values above or below the reference range will be identified in the data listings with flags for high and low values.

A listing of the normal reference ranges will be included.

7.4.4 Vital Signs

Vital signs will include oral temperature, blood pressure at rest, heart rate, and respiratory rate. Weight is summarized under physical exam. Vital signs will be assessed for change from baseline by visit. Patients with missing data for a given time point will not contribute to the tabulations for that time point. Changes from baseline values will be presented.

A listing of all vital signs will be included.

7.4.5 Physical Exam

Physical exam of the following body categories occurs at screen 1; general appearance, skin, HEENT, neck (including thyroid), heart, lungs, abdomen, lymph nodes, extremities, neurological assessment, musculoskeletal system, and other as specified on CRF. Subsequent visits require physical exam assessment only if significant change since screen 1 occurs for one of the specified body categories. Weight is recorded at Screening 1, Follow-up Month 12, and End of Study.

A listing of physical exam assessments including weight will be included.

7.4.6 Antibody Activity

A blood sample, taken at initial screening to determine patient eligibility, will be used to determine the presence of antibodies to donor SB623 cells: HLA Class I (HLA-A 36XX, HLA-A 68XX, HLA-B53XX, or HLA-B*5802) or Class II (DRB1*1101 (DR11) or DRB1*12CVT (DR12)). Serum antibody measurements are then taken throughout the study at time points indicated in Appendix 9.1.

Presence of antibodies to SB623 will be indicated in the antibody listing by patient by visit.

7.4.7 PBMC and Cytokines

PBMC function during the study will be evaluating any changes from baseline in cytokine secretion (Serum TNF-α, Plasma IL-6, and Plasma IFN-γ).

PBMC function, the cytokine secretion results, will be listed by patient by visit.

7.5 INTERIM ANALYSIS

One interim analysis is planned, which will be performed when the last patient enrolled in the study, has completed their Month 6 visit. This interim analysis will be based on the Month 6 data and will include all tables, listings, and figures.

7.6 DATA SAFETY AND MONITORING BOARD

The members of the Data Safety and Monitoring Board (DSMB) will be experts who are independent from the sponsor, formed to continuously evaluate toxicity and mortality rates. The procedures and responsibilities for the collection, analysis, and review of the data by the DSMB as well as communication and documentation of their opinions and recommendations are defined in the DSMB charter.

The DSMB will review the safety profile of all patients in each cohort. If the safety profile is deemed acceptable by the DSMB for a given cohort, the first patient in each subsequent cohort will be dosed, beginning 4 weeks after dosing of the last patient of the prior cohort. Two or more serious adverse events will trigger a review by the DSMB before continuing enrollment. Each DLT will be evaluated by the DSMB. The DSMB shall be the final arbitrator for attributions.

8. REFERENCES

1. Meinert, C. (1986). *Clinical Trials: Design, Conduct, and Analysis*. Oxford University Press, New York.
2. World Health Organization Drug Dictionary (WHODD) September 2012 (or later).
3. MedDRA dictionary, version 15.1 (or higher).

9. TABLES, LISTINGS, AND FIGURES FOR EACH COHORT AND COMBINED COHORTS

9.1 PROGRAMMING SPECIFICATIONS

Unless otherwise noted, the following conventions should be used when programming the analysis tables, listings, and figures:

- Listings should be sorted by dose group and the unique patient identifier
- Repeat footnotes on all pages of tables and listings
- Leading 0 will be shown for all values between -1 and 1.
- For the presentation of frequency and percentage data, events with the frequency of zero should be presented as the count only (i.e., presented as "0" instead of "0 (0%)").
- Percentages should be calculated based on patients with non-missing data, unless specified otherwise.
- When adverse events are reported, the MedDRA version will be reported in the footnote, similarly when medications are reported, the WHODD version will be reported in the footnote.
- The date format for all presentations will be 'DDMMMYYYY'.
- The header on all tables, listings and figures will include: Sponsor name and Protocol number(Left); Page X of Y (Right), TLF Number and Title
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10. APPENDICES

10.1 SCHEDULE OF STUDY ASSESSMENTS

	Scr. 1	Scr. 2	Baseline[1]	Enroll[2]	Cell Admin	Follow-Up Period							Last Eval.
Study Day			**-2 to-1**	**-1 to 1**	**1**	**2**	**8**						
Study Week	**-3**	**-1**	**1**	**1**	**1**	**1**	**2**						
Study Month								**End of 1 and 2**	**End of 3 and 4**	**End of 6**	**End of 9**	**End of 12**	**End of 24**
Informed Consent	X[3]												
Demographics	X												
Inclusion/Exclusion	X		X										
Medical History	X	X[4]	X[5]	X[6]									
Medication History	X	X[4]	X[5]	X[6]									
Signs & Symptoms	X	X[4]	X[5]	X[6]									
Pregnancy Test[7]	X[8]		X										
Physical Exam.	X		X									X	X
Vital Signs	X	X	X				X	X	X	X	X	X	X
Chest X-Ray and ECG	X												
Hematology	X	X	X				X	X	X	X	X	X	X
Serum Chemistry	X	X	X				X	X	X	X	X	X	X
INR	X		X										
Occult Malignancy	X												

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

	Scr. 1	Scr. 2	Baseline[1]	Enroll[2]	Cell Admin	Follow-Up Period							Last Eval.
Study Day			**-2 to-1**	**-1 to 1**	**1**	**2**	**8**						
Study Week	**-3**	**-1**	**1**	**1**	**1**	**1**	**2**						
Study Month								**End of 1 and 2**	**End of 3 and 4**	**End of 6**	**End of 9**	**End of 12**	**End of 24**
Lipid Panel			X				X	X	X	X	X	X	X
Cytokines			X				X	X (mo. 2)	X (mo. 4)	X	X	X	X
Blood for HLA antibodies	X[9]												
Head CT					X								
Imaging--Head FDG-PET			X							X		X	X
Imaging--Head MRI	X[10]		X		X[11]	X	X	X	X	X	X	X	X
Clinical Stroke Evaluations	X[12]	X[12]	X					X	X	X	X	X	X
Cognitive Questionnaire			X							X		X	X
Blood for antibodies to SB623 and for PBMCs			X				X	X (mo. 2)	X (mo. 4)	X	X	X	X
Serum Antibodies[13]			X				X	X (mo. 2)	X (mo. 4)	X	X	X	X
PBMC Function			X				X	X (mo. 2)	X (mo. 4)	X	X	X	X
Adverse Events					X	X	X	X	X	X	X	X	X
Concomitant Medications					X	X	X	X	X	X	X	X	X

[9] May also be done at a pre-Screen visit
[10] May instead be done at a pre-Screen visit
[11] Or CT overlaid with MRI from Baseline
[12] NIHSS and Modified Rankin at Scr. 1 and only NIHSS at Scr. 2
[13] Assays may be done bimonthly on pooled samples
[14] These evaluations on batched samples of PBMCs will be approximately at bimonthly intervals during the first 6 months, quarterly thereafter through the first year, then at 2 years.

10.2 CLINICALLY NOTABLE ABNORMAL VALUES

WHO (World Health Organization) Toxicity Criteria by Grade

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

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
	(mg/dl)					
Metabolic	Hypocalcaemia (mg/dl)	> 8.4	8.4 - 7.8	7.7 - 7.0	6.9 - 6.1	6
Metabolic	Hypomagnesaemia (mg/dl)	> 1.4	1.4 - 1.2	1.1 - 0.9	0.8 - 0.6	0.5
Liver	Bilirubin (N = 17 µmol/L)	WNL	-----	< 1.5 x N	1.5 - 3.0 x N	> 3.0 x N
Liver	Transaminase (SGOT, SGPT)	WNL	2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N
Liver	Alk Phos or 5 nucleotidase	WNL	< 2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N
Liver	Liver- clinical	No change from baseline	-----	-----	precoma	hepatic coma
Kidney, bladder	Creatinine	WNL	< 1.5 x N	1.5 - 3.0 x N	3.1 - 6.0 x N	> 6.0 x N
Kidney, bladder	Proteinuria	No change	1 (+) or < 0.3 g% or 3 g/L	2 - 3 (+) or 0.3 - 1.0 g% or 3 - 10 g/L	4 (+) or > 1.0 g% or > 10g/L	nephrotic syndrome

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Protocol SB-STR01

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

Statistical Analysis Plan Addendum

Final 1.0

Date: 14DEC2016

Prepared by: Jerin Ullah

Signature Page

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1. INTRODUCTION AND BACKGROUND

This document is an addendum to the Statistical Analysis Plan dated 30JAN2014 for study SB-STR01. This statistical analysis plan addendum is based on protocol amendment 4.5, dated 22 March 2013.

All statistical analyses and data presentations were performed by the biostatistics group at inVentiv Health Clinical (IHC) using SAS®, version 9.2 or higher.

2. CHANGES IN THE COMPUTATION OF FUGL-MEYER SCORES IN SB-STR01

Fugl-Meyer scores have been incorrectly recorded on the case report form (CRF) for SB-STR01. There appear to be errors in the CRF construction. This document describes the changes in the computation of the Fugl-Meyer scores and component scores to account for the errors in data collection.

2.1 Description of the Errors:

There appear to be errors in the CRF construction.

The CRFs (and thus the database) do not match the Fugl-Meyer source documents. The Fugl-Meyer source documents total up to the correct scores; however, the CRFs and the database do not.

The correct number of points possible for each individual component is as follows:

Fugl-Meyer Component	Points Possible
Motor	**100**
Upper Extremity	*66*
Lower Extremity	*34*
Sensory Function	**24**
Upper Limb	*12*
Lower Limb	*12*
Balance	**14**
Joint Range of Motion	**44**
Upper Limb	*24*
Lower Limb	*20*
Joint Pain	**44**
Upper Limb	*24*
Lower Limb	*20*
TOTAL	***226***

There are three errors that have been noted on the CRFs:

(1) In Section A, part I "Upper Extremity Reflex Activity": In the Fugl-Meyer specification document, there are two items: "Flexors-Biceps and Finger Flexors" and "Extensors-Triceps". However, in the CRFs, there are three items: "Flexor-Biceps", "Flexor-Finger Flexors", and "Extensors-Triceps". In other words, three separate scores were recorded in the CRF (and the database) when only two should have been recorded. This incorrectly increased the possible FM-Upper Extremity Motor portion by 2 points.
(2) In Section E, part I "Lower Extremity Reflex Activity": In the Fugl-Meyer specification document, there are two items: "Flexors-Knee Flexors" and "Extensors-Patellar and Achilles". However, in the CRF, there are three items: "Flexor-Hamstrings", "Flexor-Achilles", and "Extensors-Patellar". Again, three separate scores were recorded in the CRF (and the database) when only two should have been recorded. This incorrectly increased the possible FM-Lower Extremity Motor portion by 2 points.
(3) In Section E, part V "Lower Extremity Normal Reflex Activity": In the Fugl-Meyer specification document, there is one item: "Reflex Activity-Knee Flexors, Patellar, Achilles". However, in the CRF, there are three items: "Flexor-Hamstrings", "Flexor-Achilles", and "Extensors-Patellar". Thus, three separate scores were recorded in the CRF (and the database) when only one should have been recorded. This incorrectly increased the possible FM-Lower Extremity Motor portion by 4 additional points.

Plus, there is an additional programming issue that also affects the database:

- The seven items in Section G (Balance) comprise 14 possible points. Rather than being designated as their own "Balance" component score, they were mistakenly combined with the Lower Extremity Score, incorrectly increasing the possible FM-Lower Extremity Motor portion by an additional 14 points.

So, overall, the summary scores in the database are comprised of too many potential points, with errors displayed in red.

Fugl-Meyer Component	**Points Possible**
Motor	**122**
Upper Extremity	*68*
Lower Extremity	*54*
Sensory Function	**24**
Upper Limb	*12*
Lower Limb	*12*
Balance	**14**
Joint Range of Motion	**44**
Upper Limb	*24*
Lower Limb	*20*

Joint Pain	**44**
Upper Limb	*24*
Lower Limb	*20*
TOTAL	***234***

The Statistical Analysis Plan has a paragraph that describes the Fugl-Meyer correctly, and then "for the purposes of this analysis" describes how it is computed using the incorrectly collected data. It states that there are too many points in the upper and lower motor scores (from the additional questions and from incorrectly including Section G of the Fugl-Meyer in the lower motor score). So this would parallel the findings described above.

Here is the pertinent section of the SAP:

> Fugl-Meyer Scale: The Fugl-Meyer Scale is a stroke-specific, performance-based impairment index. It is designed to assess motor functioning, balance, sensation, and joint functioning. The scale is comprised of five domains and there are 155 items in total. Scoring is based on direct observation of performance. Scale items are scored on the basis of ability to complete the item using a 3-point ordinal scale where 0=cannot perform, 1=performs partially, and 2=performs fully. The total possible scale score is 226.
>
> Points are divided among the domains as follows:
>
> - Motor score: ranges from 0 (hemiplegia) to 100 points (normal motor performance).
> - Divided into 66 points for upper extremity and 34 points for the lower extremity. Total motor scores (out of 100 points) are classified based upon the following impairment severity. Total motor scores of <50 = Severe, 50-84 = Marked, 85-94 = Moderate, and 95-99 = Slight.
> - Sensation: ranges from 0 to 24 points.
> - Divided into 8 points for light touch and 16 points for position sense.
> - Balance: ranges from 0 to 14 points.
> - Divided into 6 points for sitting and 8 points for standing.
> - Joint range of motion: ranges from 0 to 44 points.
> - Joint pain: ranges from 0 to 44 points
>
> For purposes of this analysis, the total Fugl-Meyer score, the total of the upper and lower extremity motor score, the total of the upper extremity motor score and the total of the lower extremity motor score will be used. For the motor scores, the total for the upper extremity will be the total of the questions from Sections A-D of the Fugl-Meyer CRF (34 questions with a maximum score of 68 points) and the total for the lower extremity will be the total of the questions from Sections E-G of the Fugl-Meyer CRF (27 questions with a maximum score of 54 points).

2.2 Programming Changes for Final Analysis

For final analyses, there are two issues to be addressed: (a) the inclusion of the seven balance items from Section G in the lower motor extremity score; and (b) the additional items included in the CRFs for recording scores.

The first issue is easiest to address: for final analyses, the seven balance items from Section G should be removed from the FM-Motor score and the FM-Lower Extremity score.

The second issue is more difficult to address, because the CRFs were filled out differently for different subjects. It appears that four different ways of filling out the CRF may have occurred: (1) the extra item was left blank and recorded as a missing value in the database; (2) the extra item was left blank and recorded as a zero in the database; (3) the extra item was filled out with the same value as in the initial item; and (4) the extra item was evaluated independently from the original item, yielding two different scores. Although it cannot be determined for certain if blank items were assigned zero values in the database, it appears that all four of these modalities of completing the CRF may have occurred.

Thus, one way to estimate the score is to take the maximum recorded score for the three instances in which multiple scores have been recorded when there should have only been a single score. The advantage of this method is that it can be used for any of the four different modalities of completing the CRF described above and is consistent with the way the Fugl Meyer score is meant be calculated (See et al., A Standardized Approach to the Fugl-Meyer Assessment and Its Implications for Clinical Trials. Neurorehabilitation and Neural Repair. 2013; 27(8) 732–741).
It is particularly useful with a mix of true missing values and zero values that are actually missing values.

Implementing this approach would mean:

(1) In Section A, part I "Upper Extremity Reflex Activity": In the CRFs, the maximum score for the items "Flexor-Biceps" and "Flexor-Finger Flexors" would be used for the Fugl-Meyer item “Flexors-Biceps and Finger Flexors”.
(2) In Section E, part I "Lower Extremity Reflex Activity": In the CRFs, the maximum score for the items: "Flexor-Achilles” and "Extensors-Patellar" would be used of the Fugl-Meyer item "Extensors-Patellar and Achilles".
(3) In Section E, part V "Lower Extremity Normal Reflex Activity": In the CRFs, the maximum score for the items "Flexor-Hamstrings", "Flexor-Achilles", and "Extensors-Patellar" would be used for the Fugl-Meyer item "Reflex Activity-Knee Flexors, Patellar, Achilles".

The following updates were also implemented related to missing values:

1. If an post-baseline observation that is not indicated as ‘NOT DONE’ has any individual item missing, the last-observation-carried-forward (LOCF) method will

be used to impute missing items, i.e. the results of the item from previous available observation of the same subject is used for imputing the missing results.

2. If a baseline record has any missing individual scores, they were handled in two ways:
   a. imputed with 0
   b. imputed with first observed post-baseline values

However, in final data, all missing baseline items either have 0 as first observed post-baseline values, or do not have any non-missing post-baseline values. Therefore results of approach b is not presented separately from results of approach a as they would be identical.

The imputation of missing values has the exceptions as described in 3 below, in which cases missing are deemed as legitimate.

3. According to Fugl-Meyer Score document, Section A, Part V 'Normal reflex activity' is evaluated only if full score of 6 points achieved on Part IV; and Section E, Part V 'Normal reflex activity' is evaluated only if full score of 4 points achieved on Part IV. However, some records have Part V scores available even though they did not achieve full points on Part IV. An update was made so that when calculating total score and motor score, the score of part V would be excluded, if a full score was not achieved in Part IV, for each of Section A and Section E.