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Mesenchymal Stromal Cell Implants for Chronic Motor Deficits After Traumatic Brain Injury

Post Hoc Analysis of a Randomized Trial

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Abstract

Background and Objectives

Traumatic brain injury (TBI) is frequently characterized by chronic motor deficits. Therefore, this clinical trial assessed whether intracranial implantation of allogeneic modified mesenchymal stromal (SB623) cells can improve chronic motor deficits after TBI.

Methods

Post hoc analysis of the double-blind, randomized, prospective, surgical sham-controlled, phase 2, STEMTRA clinical trial (June 2016 and March 2019) with 48 weeks of follow-up was conducted. In this international, multicenter clinical trial, eligible participants had moderate-to-severe TBI, were ≥12 months postinjury, and had chronic motor deficits. Participants were randomized in a 1:1:1:1 ratio to stereotactic surgical intracranial implantation of SB623 cells (2.5×10^6, 5.0×10^6, 10×10^6) or surgical sham-controlled procedure. The prespecified primary efficacy end point was significantly greater change from baseline of the Fugl-Meyer Motor Scale (FMMS) score, a measure of motor status, for the SB623 pooled vs control arm at 24 weeks.

Results

A total of 211 participants were screened, 148 were excluded, and 63 underwent randomization, of which 61 (97%; mean age, 34 [SD, 12] years; 43 men [70.5%]) completed the trial. Single participants in the SB623 2.5×10^6 and 5.0×10^6 cell dose groups discontinued before surgery. Safety and efficacy (modified intent-to-treat) were assessed in participants who underwent surgery (N = 61; SB623 = 46, controls = 15). The primary efficacy end point (FMMS) was achieved (least squares mean [SE] SB623: +8.3 [1.4]; 95% CI 5.5–11.2 vs control: +2.3 [2.5]; 95% CI −2.7 to 7.3; $p = 0.04$), with faster improvement of the FMMS score in SB623-treated groups than in controls at 24 weeks and sustained improvement at 48 weeks. At 48 weeks, improvement of function and activities of daily living (ADL) was greater, but not significantly different in SB623-treated groups vs controls. The incidence of adverse events was equivalent in SB623-treated groups and controls. There were no deaths or withdrawals due to adverse events.

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Class of Evidence
Criteria for rating therapeutic and diagnostic studies
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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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Glossary

ADL = activities of daily living; **ARAT** = Action Research Arm Test; **DRS** = Disability Rating Scale; **FMMS** = Fugl-Meyer Motor Scale; **GOS-E** = Glasgow Outcome Scale-Extended; **GV** = gait velocity; **mITT** = modified intent-to-treat; **MMRM** = mixed model of repeated measures; **STEMTRA** = Stem Cell Therapy for Traumatic Brain Injury; **TBI** = traumatic brain injury; **TEAE** = treatment-emergent adverse event; **TESAE** = treatment-emergent serious adverse event.

Discussion

Intraparenchymal implantation of SB623 cells was safe and significantly improved motor status at 24 weeks in participants with chronic motor deficits after TBI, with continued improvement of function and ADL at 48 weeks. Cell therapy can modify chronic neurologic deficits after TBI.

Trial Registration Information

ClinicalTrials.gov Identifier: NCT02416492. Submitted to registry: April 15, 2015. First participant enrolled: July 6, 2016. Available at: classic.clinicaltrials.gov/ct2/show/NCT02416492.

Classification of Evidence

This study provides Class I evidence that intracranial implantation of allogeneic stem (SB623) cells in adults with motor deficits from chronic TBI improves motor function at 24 weeks.

Introduction

Traumatic brain injury (TBI) is recognized among worldwide trauma-related injuries as the greatest contributor to death and disability.[1] In 2018, the global incidence of all-cause, all-severity TBI was estimated to be 69 million cases per year while in 2016, the global prevalence of chronic impairment secondary to TBI was estimated to be 55.5 million cases.[2,3] Advances in acute clinical care have improved post-TBI survival rates, yet there are no approved therapies for TBI, and many participants experience lifelong disabilities as shown by static return-to-work rates over the past 50 years.[4-8]

The prevalence of TBI-related long-term disabilities varies around the world, ranging from 1,766 per 100,000 persons in the United States to 704 per 100,000 persons in France.[9,10] In the United States, long-term motor deficits are reported to be experienced by approximately 43% of participants who were hospitalized with TBI while approximately 5.3 million people live with a TBI-related disability.[11,12] In addition, more than one-third of participants with severe TBI are reported to have at least 1 neuromotor impairment 2 years after acute rehabilitation.[13] Despite improvements in the treatment of acute TBI, long-term motor deficits secondary to TBI remain a major unmet medical need.

The potential of cell therapies to be safe and effective treatments for the recovery of impairments that are associated with chronic TBI has been demonstrated in several early-stage clinical studies.[14-17] Allogeneic modified bone marrow–derived mesenchymal stromal (SB623) cells are in clinical development for chronic motor deficits (e.g., hemiparesis beyond 1 year after injury) secondary to TBI and stable ischemic stroke (SanBio, Inc., Mountain View, CA). In a 2-year phase 1/2a study (NCT01287936), intracerebral implantation of SB623 cells in participants with chronic ischemic stroke was safe and associated with sustained significant improvement of measures of motor status.[18]

In the primary analysis at 24 weeks of the 1-year, double-blind, randomized, surgical sham-controlled, phase 2 "Stem Cell Therapy for Traumatic Brain Injury" (STEMTRA) trial (NCT02416492), which investigated the intracerebral implantation of SB623 cells in participants with chronic motor deficits after TBI, the authors reported comparable rates of adverse events in both the SB623 pooled and control arms, and that the primary efficacy end point of significantly greater change from baseline of the Fugl-Meyer Motor Scale (FMMS) score was achieved for the SB623 pooled vs control arms at 24 weeks.[17] However, secondary end points of improvement of function and activities of daily living (ADL) did not significantly change from baseline for the SB623 pooled vs control arms at 24 weeks.[17]

In this report, we present a post hoc analysis from the completed STEMTRA trial (additional data at ClinicalTrials.gov: NCT02416492), in which we aimed to assess whether implantation of SB623 cells in participants was safe and could improve chronic motor deficits after TBI at 48 weeks.

The primary research objective of the STEMTRA trial was to evaluate the clinical efficacy of intracerebral implantation of SB623 cells on chronic motor deficits secondary to TBI at 24 weeks after implantation. The secondary research objectives of the STEMTRA trial were to evaluate (1) the effect of intracerebral implantation of SB623 cells on disability

Table 1 Study Inclusion and Exclusion Criteria[a]

Inclusion criteria
- Age 18–75 y
- Documented history of TBI, with correlated MRI or CT
- At least 12 mo after TBI
- Focal cerebral injury able to be identified on MRI (±concomitant diffuse axonal injury)
- Neurologic motor deficit substantially due to focal cerebral injury observed on MRI
- GOS-E scores of 3–6 (i.e., moderate or severe disability)
- Require Motricity Index upper extremity score of 10–81 (at least 2 scores less than 33 with 1 of these less than 25 and at least 1 score greater than 0) and/or a lower extremity score of 10–78 (at least 2 scores less than 33 with 1 of these less than 25 and at least 1 score greater than 0)
- Able and willing to undergo CT and MRI
- Must have agreed to the use of antiplatelet, anticoagulant, or nonsteroidal anti-inflammatory drugs in accordance with the anticoagulant guidelines[29]
- Participants must be willing to participate in study-related exercises to the extent possible
- Must have been willing to discontinue herbal or nontraditional medicines 1 wk before and 1 wk after the surgical procedure
- Ability to undergo all planned neurologic assessments
- Ability of the participant or legal authorized representative to understand and sign an informed consent

Exclusion criteria
- History or presence of any other major neurologic diseases
- Any seizures in the previous 3 mo
- The presence of contracture at any joints that would have interfered with interpretation of any of the neurologic assessments (e.g., contracture preventing the detection of any increase in the range of motion or ability to perform a task)
- Other neurologic, neuromuscular, or orthopaedic diseases that limited motor function
- Clinically significant finding on MRI of the brain not related to TBI
- Known presence of any malignancy except squamous or basal cell carcinoma of the skin
- History of CNS malignancy
- Positive findings on tests for occult malignancy, unless a nonmalignant etiology is confirmed
- Uncontrolled systemic illness, including but not limited to hypertension (systolic >150 mm Hg or diastolic >95 mm Hg); diabetes; and renal, hepatic, or cardiac failure
- Uncontrolled major psychiatric illness, including depression symptoms (CESD-R Scale score of ≥16)
- Total bilirubin >1.9 mg/dL
- Serum creatinine >1.5 mg/dL
- Hemoglobin <10.0 g/dL
- Absolute neutrophil count <2,000/mm^3
- Absolute lymphocytes <800/mm^3
- Platelet count <100,000/mm^3
- Liver disease documented by AST (SGOT) or ALT (SGPT) ≥2.5× institutional upper limit of normal
- Serum calcium >11.5 mg/dL
- Unexplained abnormal preoperative test values (blood tests, ECG, chest X-ray); x-ray evidence of infection; uncontrolled atrial fibrillation or uncontrolled congestive heart failure
- Presence of craniectomy (without bone flap replacement) or other contraindications to stereotactic surgery
- Participation in any other investigational trial within 4 wk of initial screening or within 7 wk of study entry
- Botulinum toxin injection, phenol injection, intrathecal baclofen, or any other interventional treatments of spasticity (except bracing and splinting) within 16 wk of the baseline visit (interventional treatment refers to treatment given with special equipment, which is typically performed in a surgical or procedural type facility—this does not apply to oral medications such as oral baclofen)
- Ongoing use of herbal or other nontraditional drugs
- Substance use disorder (per DSM-V criteria, including drug or alcohol)
- Contraindications to head CT or MRI
- Pregnant or lactating
- Women of childbearing potential unwilling to use an adequate birth control method during the 12 mo of the study
- Any other condition or situation that the investigator believed may interfere with the safety of the participant or the intent and conduct of the study
- Participants with allergic reactions to the ingredients of SB623, the drugs used when administering SB623, or the drugs used in testing (applicable for Japan only)

[a] This table was originally presented as Table 1 in the study by Kawabori M, Weintraub AH, Imai H, et al. Cell therapy for chronic TBI: interim analysis of the randomized controlled STEMTRA trial. Neurology. 2021;96(8):e1202-e1214. doi:10.1212/WNL.0000000000011450.

parameters and (2) the safety and tolerability of intracerebral implantation of SB623 cells.

Methods

In this report, we present a post hoc analysis of the final 1-year data from the completed STEMTRA trial. Participant baseline characteristics, inclusion and exclusion criteria, data analysis methods, and design of the STEMTRA trial have been described previously in the primary analysis,[17] which reported the primary efficacy and secondary end points at 24 weeks. In addition, inclusion and exclusion criteria are delineated in detail in Table 1. CONSORT reporting guidelines were used in the reporting of this study.[19]

Study Population, Standard Protocol Approvals, Registrations, and Participant Consents

The STEMTRA trial (ClinicalTrials.gov: NCT02416492) enrolled participants with moderate or severe TBI with a Motricity Index upper extremity score of 10–81 (at least 2 scores less than 33 with 1 of these less than 25 and at least 1 score greater than 0) and/or a lower extremity score of 10–78 (at least 2 scores less than 33 with 1 of these less than 25 and at least 1 score greater than 0); with Glasgow Outcome Scale-Extended (GOS-E) scores of 3–6; aged 18–75 years; who were at least 12 months postinjury; and who had chronic motor deficits (e.g., hemiparesis beyond 1 year after injury) that correlated with MRI-observed focal cerebral injury. Participants were instructed on a set of standardized physical therapy exercises (cylinder grasp, thumb raise, stand and squat, walk), which were performed at home each morning and afternoon during the screening period and for the first 6 months of the study. The trial was conducted between June 2016 and March 2019 at a total of 27 sites (21 sites in the United States, 5 sites in Japan, and 1 site in Ukraine). Individual institutional review boards reviewed and approved clinical protocols, and participants or legal authorized representatives provided written informed consent.

SB623 Cells

SB623 cells are allogeneic modified bone marrow–derived mesenchymal stromal cells, which are produced by transient

transfection with a plasmid containing the intracellular domain of human *Notch-1*.[20] SB623 cells are produced in a Good Gene, Cellular, and Tissue-based Product Manufacturing Practice facility (Lonza Biologics, Portsmouth, NH). Details of the preparation of SB623 cells have been described previously.[18]

Randomization and Design

A total of 211 survivors were screened by clinical sites for the STEMTRA trial, of whom 63 participants with stable chronic motor deficits secondary to TBI were randomized using a block size of 4 with an interactive web response system on the day of the surgery. For participants enrolled outside Japan, randomization was stratified by the GOS-E score (i.e., scores 3, 4, 5, or 6); for participants in Japan, randomization was not stratified. The surgeons, cell preparation staff, and operating room staff only became aware of treatment group allocation after randomization. Communication between surgeons and efficacy raters was strictly prohibited. Efficacy raters and study participants were blinded to treatment. Participants were randomized in a parallel 1:1:1:1 ratio to the intent-to-treat population, with 3 SB623-treated groups each having 16 participants receiving single doses of 2.5×10^6, 5.0×10^6, or 10×10^6 cells and a sham surgery control arm with 15 participants (Figure 1). Surgeons were unable to determine safe stereotactic implantation trajectories in 2 participants (1 in the SB623 2.5×10^6 and 1 in the SB623 5.0×10^6 cell dose group); therefore, these participants discontinued from the trial before surgery. As a result, 61 participants enrolled in the STEMTRA trial formed both the modified intent-to-treat (mITT) and safety populations (baseline demographics, Table 2). In this final post hoc analysis, all 61 participants in the mITT and safety populations had completed 48-week evaluations.

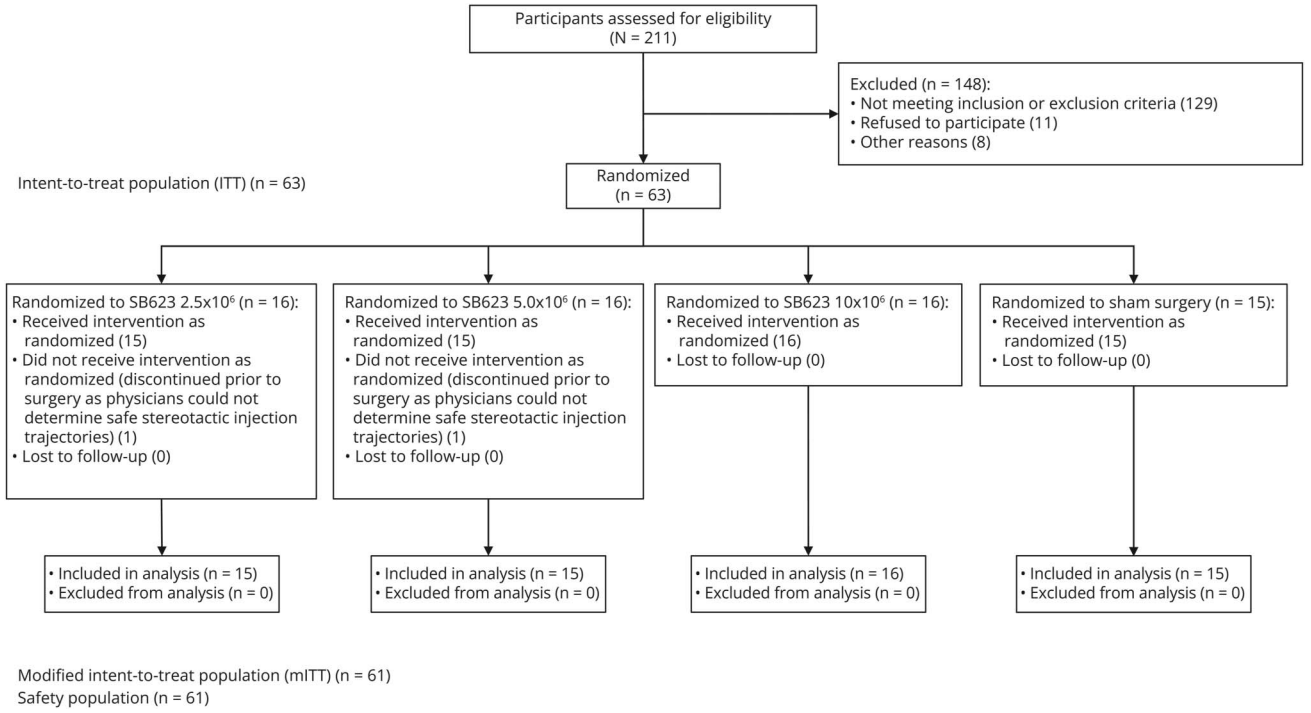
Sample Size Calculation

A sample size of 48 participants (36 in the SB623 treatment arm and 12 in the control arm) was determined as an appropriate sample size. This required a 2-sample *t* test to show superiority of the SB623 pooled arm over sham control, assuming 80% power, alpha of 0.05, a 2-tailed test, and 3:1 randomization. This assumed that the mean change from baseline at 24 weeks in the FMMS score was 10 points for the SB623 treatment arm and 3 points for the control arm, with an assumed SD of 7.25 per arm. Based on an 8% upward adjustment to compensate for dropout participants, a total of approximately 52 participants were required. The primary analysis was conducted at 24 weeks and the final post hoc analysis at 48 weeks after implantation follow-up.

Stereotactic Surgical Procedure

SB623 cells were implanted into participants using a stereotactic surgical procedure by burr-hole craniostomy to the peritrauma brain tissue area responsible for the motor deficits

Figure 1 CONSORT Flow Diagram



63 participants were randomized to SB623 cell treatment or sham surgery. However, safe stereotactic implantation trajectories could not be determined for 1 participant in the SB623 2.5×10^6 cell dose group and 1 participant in the SB623 5.0×10^6 cell dose group, resulting in both participants discontinuing from the trial before surgery. Both the modified intent-to-treat (mITT) and safety populations (n = 61) contained participants who were randomized and underwent SB623 cell treatment or sham surgery. All 61 participants completed 48-week evaluations.

Table 2 Baseline Demographics of Modified Intent-to-Treat and Safety Populations[a]

Characteristic	SB623 cell dose/implantation					
	2.5×10^6 (n = 15)	5×10^6 (n = 15)	10×10^6 (n = 16)	Pooled (n = 46)	Control (n = 15)	Total (N = 61)
Age (y)						
Mean (SD)	36.7 (13.6)	31.2 (9.2)	34.2 (11.5)	34.0 (11.5)	35.5 (13.0)	34.4 (11.8)
Median	34.0	30.3	30.2	32.6	35.4	33.4
Range (min–max)	19.8–65.2	18.5–53.1	18.9–53.0	18.5–65.2	18.8–67.5	18.5–67.5
Sex, n (%)						
Male	11 (73.3)	12 (80.0)	11 (68.8)	34 (73.9)	9 (60.0)	43 (70.5)
Female	4 (26.7)	3 (20.0)	5 (31.3)	12 (26.1)	6 (40.0)	18 (29.5)
Time since injury (mo)						
Mean (SD)	103.9 (68.0)	82.0 (67.9)	94.3 (76.4)	93.6 (10.6)	99.3 (23.1)	95.0 (9.7)
Median	86.5	42.6	69.7	72.9	62.4	68.9
Range (min–max)	20.2–242.2	19.0–240.1	16.8–341.2	16.8–341.2	28.0–336.7	16.8–341.2
Race, n (%)						
White	11 (73.3)	9 (60.0)	11 (68.8)	31 (67.4)	11 (73.3)	42 (68.9)
Black	0 (0.0)	1 (6.7)	0 (0.0)	1 (2.2)	0 (0.0)	1 (1.6)
Asian	4 (26.7)	5 (33.3)	5 (31.3)	14 (30.4)	4 (26.7)	18 (29.5)
Ethnicity, n (%)						
Hispanic or Latino	0 (0.0)	1 (6.7)	1 (6.3)	2 (4.3)	0 (0.0)	2 (3.3)
Not Hispanic or Latino	15 (100)	14 (93.3)	15 (93.8)	44 (95.7)	15 (100)	59 (96.7)

[a] This table is based on data that were originally presented in Table 2 of the study by Kawabori M, Weintraub AH, Imai H, et al. Cell therapy for chronic TBI: interim analysis of the randomized controlled STEMTRA trial. Neurology. 2021;96(8):e1202-e1214. doi:10.1212/WNL.0000000000011450.

as identified by MRI and described previously.[18] Sham surgery control participants received a similar stereotactic burr-hole surgical procedure without penetration of the inner table or dura mater, followed by surgical closure of the scalp to maintain blinding of the participant and clinical efficacy and safety assessors.

Study Visit Schedule

STEMTRA trial participants attended the following visit schedule: screen (study day −84 to −15); baseline (study day −14 to −1); cell implantation or sham surgical procedure (day 1); visits (days 2, 8; months 1, 3, 6, 9); final visit (month 12). Clinical TBI evaluations were performed at baseline and months 1, 3, 6, 9, and 12.

Trial Blinding

Efficacy assessments were performed by site-specific neurologists, physiatrists, and physical therapists who were trained in the assessments, and training certification was confirmed and documented by the clinical research organization, with recertification occurring every 6 months; all health care professionals evaluating efficacy were blind to participant treatment. Treatment-emergent adverse events were evaluated by rehabilitation physicians who were also blind to participant treatment. Unblinding events occurred to 2 study participants and their caregivers; however, in both cases, health care professionals who evaluated efficacy remained blind to the participant treatment group.

Efficacy End Points

The focus of SB623 cells is to treat participants with chronic TBI who have persistent deficits in the motor domain of neurologic function; as such, the STEMTRA trial end points addressed the 3 primary levels of human functioning consistent with the World Health Organization's International Classification of Functioning, Disability and Health: (1) impairment (body function and structure); (2) disability (activity); and (3) handicap (participation).[21]

Impairment was assessed using the FMMS, a broadly accepted measure of motor impairment, as the primary efficacy end point at 24 weeks.[22-24] Disability was assessed using the Action Research Arm Test (ARAT) and gait velocity (GV), measures of upper and lower extremity motor functions, respectively.[25-27] Handicap was assessed using NeuroQOL upper and lower extremity function T scores (NeuroQOL

upper and lower scores), measures of ADL and mobility, respectively.[28] Global outcome was assessed using the Disability Rating Scale (DRS) to track general functional change over time.[29] The secondary end points were DRS, ARAT, GV, and NeuroQOL upper and lower scores and Global Rating of Perceived Change, each at 24 weeks.[17] In this post hoc analysis, FMMS, DRS, ARAT, GV, and NeuroQOL upper and lower scores were assessed at 48 weeks.

Safety

Treatment-emergent adverse events (TEAEs) were assessed and reported by study investigators and were defined as any event that was not present before the initiation of cell treatment or surgical procedure, or any event that was already present which worsened in either intensity or frequency after exposure to cell treatment or surgical procedure. TEAEs were graded as follows: (1) mild, (2) moderate, (3) severe, or (4) life-threatening. The relationship between TEAEs and cell treatment or surgical procedure was determined by the investigator's clinical judgment, using guidance from eTable 1. Participants were instructed to report TEAEs spontaneously or in response to nondirected questioning, with TEAE reporting starting when survivors were assessed for eligibility and finishing 12 months after SB623 cell treatment.

Statistics

Categorical variables were summarized by frequencies and percentages in each category. Descriptive statistics were calculated for continuous variables, including participant number, mean, SD, median, minimum, and maximum.

For efficacy end points in this post hoc analysis, a mixed model of repeated measures (MMRM) using an unstructured covariance matrix for the restricted maximum likelihood estimation procedure was used to compare the SB623 pooled with control arms and SB623 5×10^6 cell dose with control arms. The MMRM model included the following terms: treatment, visit, treatment-by-visit interaction, baseline score, baseline score–by-visit interaction, GOS-E score at screening, and GOS-E score at screening–by-visit interaction. In addition, for efficacy end points, a post hoc responder analysis of SB623 pooled participants was conducted for participants who achieved a change of the FMMS score from baseline of ≥8 at 24 and 48 weeks (responder vs nonresponder).

For safety comparisons, the Fisher exact test was used to analyze the percentage of participants experiencing at least 1 TEAE.

$p = 0.05$ was considered as statistically significant. Data analyses were performed using SAS version 9.4 (Cary, NC).

Data Availability

Individual deidentified participant data, study protocol, statistical analysis plan, clinical study report, and informed consent forms will be available to qualified external medical and scientific researchers. Data sharing requests may be submitted on publication of this article, with no end date for eligibility. Qualified medical and scientific researchers may submit a data sharing request containing research objectives, data requirements, statistical analysis plan, end points/outcomes of interest, scientific value and impact, and a publication plan to the Chief Medical Officer of SanBio, Inc. The scientific appropriateness of the request will be reviewed by SanBio, Inc.

The study protocol and statistical analysis plan for the STEMTRA trial are available in eSAP 1.

Results

Efficacy Outcomes

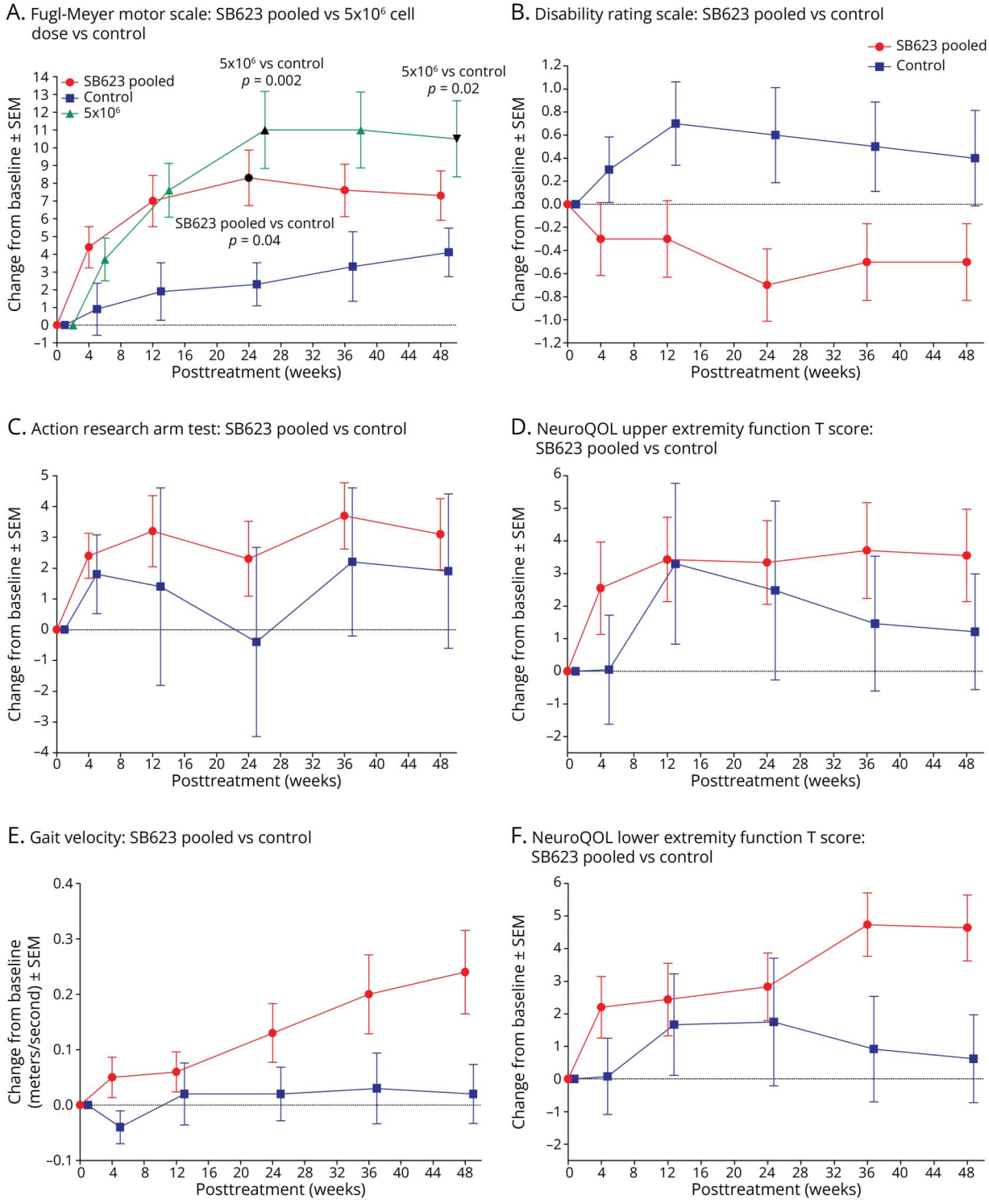
The primary efficacy end point of significantly greater change of the FMMS score from baseline at 24 weeks for the SB623 pooled vs control arm was achieved (least squares mean [SE] SB623: +8.3 [1.4]; 95% CI 5.5–11.2 vs control: +2.3 [2.5]; 95% CI −2.7 to 7.3; $p = 0.04$),[17] with SB623-treated participants experiencing higher scores and faster paced improvement of the FMMS score compared with controls at 24 weeks and sustained improvement at 48 weeks after treatment (Figure 2A).

Participants treated with the SB623 5×10^6 cell dose (n = 15) had significantly greater change of the FMMS score from baseline vs control at 24 weeks (SB623 5×10^6 cell dose: +10.9 [1.8]; 95% CI 7.3–14.6 vs control: +2.4 [1.8]; 95% CI −1.2 to 6.0; $p = 0.002$) and 48 weeks (SB623 5×10^6 cell dose: +10.5 [1.8]; 95% CI 6.7–14.3 vs control: +4.1 [1.8]; 95% CI 0.3–7.9; $p = 0.02$) (Figure 2A).

Although pooled SB623-treated participants experienced improvement of the FMMS score from baseline at 48 weeks, this was not significantly different from control (SB623: +7.5 [1.3]; 95% CI 4.9–10.1 vs control: +4.1 [2.2]; 95% CI −0.3 to 8.6; $p = 0.20$). Notably, change of the FMMS score from baseline was significant for the SB623-treated participants but not control participants at 24 and 48 weeks.

At 48 weeks, the DRS score was not significantly improved from baseline in both the SB623 pooled and control arms, although the point estimate of improvement in the SB623 pooled arm was greater than in the control arm (SB623: −0.3 [0.2]; 95% CI −0.8 to 0.1 vs control: −0.1 [0.4]; 95% CI −0.9 to 0.7; $p = 0.61$) (Figure 2B). At 48 weeks, ARAT (SB623: +3.1 [1.2]; 95% CI 0.6–5.7 vs control: +1.8 [2.1]; 95% CI −2.5 to 6.1; $p = 0.59$) (Figure 2C), NeuroQOL upper (SB623: +3.6 [1.2]; 95% CI 1.2–6.1 vs control: +1.2 [2.1]; 95% CI −3.1 to 5.4; $p = 0.32$) (Figure 2D), GV (SB623: +0.26 [0.06]; 95% CI 0.13–0.38 vs control: +0.05 [0.11]; 95% CI −0.17 to 0.27; $p = 0.32$) (Figure 2E), and NeuroQOL lower (SB623: +4.6 [0.9]; 95% CI 2.8–6.5 vs control: +1.0 [1.7]; 95% CI −2.3 to 4.4, $p = 0.07$) (Figure 2F) scores were significantly improved from baseline in

Figure 2 SB623 Efficacy End Point Measures



(A) FMMS mean change from baseline for (1) the SB623 pooled arm at 24 weeks (●), (2) SB623 5 × 10^6 cell dose at 24 weeks (▲), and (3) SB623 5 × 10^6 cell dose at 48 weeks (▼). FMMS baseline mean (SD) scores were 52.2 (19.3) for SB623 pooled, 51.3 (22.0) for the 5 × 10^6 cell dose, and 52.3 (15.1) for sham surgery control. The graphs show data from the modified intent-to-treat population, which included 61 participants who underwent surgery. (B) DRS baseline mean (SD) scores were 4.8 (3.0) for SB623 pooled and 3.7 (2.0) for sham surgery control. The graph shows data from the modified intent-to-treat population, which included 61 participants who underwent surgery. (C) ARAT baseline mean (SD) scores were 19.1 (19.5) for SB623 pooled and 20.1 (17.2) for sham surgery control. The graph shows data from the modified intent-to-treat population, which included 61 participants who underwent surgery. (D) NeuroQOL upper baseline mean (SD) scores were 32.5 (12.9) for SB623 pooled and 32.2 (9.2) for sham surgery control. The graph shows data from the modified intent-to-treat population, which included 61 participants who underwent surgery. (E) Gate velocity baseline mean (SD) scores were 0.67 (0.49) m/s for SB623 pooled and 0.81 (0.58) m/s for sham surgery control. The graph shows data from the lower extremity deficit population (N = 56). (F) NeuroQOL lower baseline mean (SD) scores were 41.5 (10.4) for SB623 pooled and 44.3 (9.6) for sham surgery control. The graph shows data from the modified intent-to-treat population, which included 61 participants who underwent surgery. ARAT = Action Research Arm Test; DRS = Disability Rating Scale; FMMS = Fugl-Meyer Motor Scale.

the SB623 pooled arm, and the point estimates were greater than in the control arm; however, differences between the SB623 pooled and control arms were not statistically significant.

In a post hoc responder analysis of SB623 pooled participants defined by a FMMS change from baseline of ≥8 points at 24 weeks (defined as the FMMS minimally clinically important difference in chronic TBI),[30] improvement of DRS, ARAT, GV, and NeuroQOL upper and lower scores was consistently greater in the responder group than in the nonresponder group at 24 and 48 weeks (Table 3).

In addition, there were no clear relationships between FMMS change from baseline at 24 and 48 weeks and time since injury for both the SB623 pooled (mean [SD] 93.6 [10.6] months) and control arms (99.3 [23.1] months).

Safety Outcomes

At 48 weeks, each SB623-treated and control participant experienced at least 1 TEAE, with headache being the most commonly reported TEAE (SB623: 23 participants [50%] vs control: 5 participants [33.3%]) (eTable 2). Overall, there was no significant difference in the rate of TEAEs between SB623 pooled and control participants ($p = 0.25$), and there was no relationship between the frequency of TEAEs and SB623 cell dose. For both SB623-treated and control participants, greater than 90% of TEAEs were not related or unlikely to be related to cell treatment while greater than 30% of TEAEs were possibly, probably, or definitely related to the surgical procedure (Table 4). TEAEs occurring by relationship to cell treatment and surgical procedure can be found in eTables 3 and 4, respectively.

Through 48 weeks, treatment-emergent serious adverse events (TESAEs) were experienced by 4 SB623-treated participants (8.7%) (6 TESAEs) compared with 3 control participants (20%) (3 TESAEs) (Table 5). Most of the TESAEs were not related to cell treatment and were not related or unlikely to be related to the surgical procedure (Table 5). At 48 weeks, all TESAEs had resolved with the exception of worsening of poor balance experienced by Participant 4, which was ongoing.

In the trial, 4 participants had preexisting anti-SB623 HLA antibodies and a single participant without preexisting anti-SB623 HLA antibodies developed posttreatment anti-SB623 antibodies (a possible sensitization response). At 48 weeks, there were no clinically meaningful trends in vital signs or hematologic or biochemical parameters and no apparent relationships between anti-SB623 HLA antibodies and SB623 cell dose, anti-SB623 HLA antibodies and TESAEs, and anti-SB623 HLA antibodies and efficacy end points. Furthermore, there were no deaths or dose-limiting toxicities, and no participants withdrew because of adverse events.

Classification of Evidence

This study provides Class I evidence that intracranial implantation of allogeneic stem (SB623) cells in adults with motor deficits from chronic TBI improves motor function at 24 weeks.

Table 3 SB623 Efficacy End Points at 24 and 48 Weeks by FMMS Responder Status (SB623 Pool Responder: FMMS Change From Baseline ≥8 Points at 24 Weeks)

	SB623 pooled responder			SB623 pooled nonresponder		
Mean (SD)	**Baseline**	**CFB 24 Weeks**	**CFB 48 Weeks**	**Baseline**	**CFB 24 Weeks**	**CFB 48 Weeks**
FMMS	50.0 (16.4)	18.0 (8.1)	15.6 (6.2)	54.0 (21.4)	1.0 (4.7)	1.3 (6.0)
	n = 20	n = 20	n = 19	n = 26	n = 26	n = 26
DRS	5.2 (4.1)	−0.9 (2.8)	−0.9 (2.8)	4.6 (2.0)	−0.5 (1.4)	−0.3 (1.5)
	n = 19	n = 19	n = 18	n = 26	n = 26	n = 26
ARAT	25.0 (21.8)	5.6 (8.6)	6.1 (8.9)	21.8 (22.3)	−0.7 (5.0)	0.4 (3.8)
	n = 20	n = 20	n = 19	n = 26	n = 26	n = 26
GV (m/s)	0.691 (0.532)	0.263 (0.330)	0.400 (0.572)	0.621 (0.453)	0.026 (0.282)	0.116 (0.300)
	n = 20	n = 20	n = 18	n = 25	n = 25	n = 25
NeuroQOL upper	29.55 (13.45)	4.83 (9.43)	5.53 (8.46)	37.14 (11.80)	1.57 (6.21)	2.35 (8.96)
	n = 20	n = 20	n = 19	n = 26	n = 26	n = 26
NeuroQOL lower	39.65 (10.38)	4.33 (5.41)	5.85 (6.07)	41.79 (10.34)	1.39 (7.29)	3.54 (6.54)
	n = 20	n = 20	n = 19	n = 26	n = 26	n = 26

Abbreviations: ARAT = Action Research Arm Test; CFB = change from baseline; DRS = Disability Rating Scale; FMMS = Fugl-Meyer Motor Scale; GV = gait velocity.

Table 4 Unique Treatment-Emergent Adverse Events Related to Cell Treatment and Surgical Procedure

Treatment group	Not related (%)	Unlikely related (%)	Possibly related (%)	Probably related (%)	Definitely related (%)	Total number of events, n (%)
Relationship to cell treatment						
SB623	74.8	19.1	5.3	0.8	0	246 (100)
Control	75.3	19.8	4.9	0	0	81 (100)
Relationship to surgical procedure						
SB623	54.9	6.9	12.6	13.0	12.6	246 (100)
Control	59.3	9.9	14.8	3.7	12.3	81 (100)

Discussion

In this randomized trial, intraparenchymal implantation of SB623 mesenchymal stromal cells significantly improved motor status at 24 weeks (the primary efficacy end point) in participants with chronic deficits after TBI, with continued improvement of function and ADL scores at 48 weeks in this post hoc analysis, compared with control participants. SB623 cell implantation was safe and well tolerated.

The FMMS is a broadly accepted measure of motor impairment that is widely used to assess chronic stroke clinical trials.[18,22-24,31,32] In the STEMTRA trial, the primary efficacy end point of significantly greater change of the FMMS score from baseline at 24 weeks for the SB623-treated pooled vs control arms was achieved, with SB623-treated pooled participants experiencing faster paced improvement at 24 weeks compared with control participants. In a post hoc analysis, SB623-treated pooled participants experienced sustained improvement of FMMS scores at 48 weeks; however, these were not significantly different compared with control participants. The improvement of FMMS scores from baseline for control participants between 24 and 48 weeks may be the residual effect of the standardized physical therapy exercises that were performed by all participants for the first 24 weeks of the study. Notably, FMMS change from baseline was significant for SB623-treated pooled participants but not for control participants at both 24 and 48 weeks.

Participants treated with the SB623 5×10^6 cell dose experienced significantly greater change of FMMS scores from baseline compared with control at 24 and 48 weeks. Moreover, participants treated with the SB623 5×10^6 cell dose experienced faster paced improvement of motor scores than control participants, which peaked at 24 weeks and was sustained to 48 weeks. Consistent with our primary report,[17] these findings suggest that the SB623 5×10^6 cell dose also gave the most favorable outcomes at 48 weeks.

Efficacy end points of ARAT, GV, and NeuroQOL upper and lower scores that assessed function and ADL were significantly improved from baseline in the SB623-treated pooled arm but were not significantly different from those in the control arm at 48 weeks. Further improvements in function or

Table 5 Treatment-Emergent Serious Adverse Events

Cell dose/ implantation	Serious adverse event	Relationship to cell treatment	Relationship to surgical procedure
2.5×10^6	Participant 1: delirium (postoperative days 3–7)	Not related	Not related
5×10^6	Participant 2: transient ischemic attack (postoperative days 97–106)	Not related	Not related
10×10^6	Participant 3: seizure (postoperative day 66–67)	Unlikely related	Possibly related
10×10^6	Participant 3: seizure (postoperative day 360–367)	Not related	Not related
10×10^6	Participant 4: delirium (postoperative days 1–3)	Possibly related	Probably related
10×10^6	Participant 4: worsening of poor balance (postoperative day 136 and ongoing)	Unlikely related	Probably related
Control	Participant 5: wound infection (postoperative days 153–170)	Not related	Definitely related
Control	Participant 6: bicycle fall (accident) (postoperative days 148–149)	Not related	Not related
Control	Participant 7: seizure (postoperative day 227)	Unlikely related	Unlikely related

ADL may require more aggressive rehabilitation in addition to tissue regeneration, remodeling, or repair by cell therapy to produce greater degrees of functional recovery.[33]

Improvement of DRS, ARAT, GV, and NeuroQOL upper and lower scores was greater in a post hoc responder subgroup of SB623 pooled participants who achieved a FMMS change from baseline of ≥8 points at 24 weeks, than in the non-responder group, suggesting that improvement of motor impairment could lead to improvements of function and ADL. It is also noteworthy that the STEMTRA trial was not powered to detect change in DRS, ARAT, GV, and NeuroQOL upper and lower scores, and that ARAT and NeuroQOL upper and lower scores had ceiling and floor effects that reduced sensitivity.

Consistent with 24-week primary data, there was no significant difference in the rate of treatment-emergent adverse events between SB623 pooled and control participants at 48 weeks, with headache being the most commonly reported adverse event.[17] Consistent with earlier studies, greater than 90% of TEAEs were not related or unlikely to be related to cell treatment while greater than 30% of TEAEs were possibly, probably, or definitely related to the stereotactic surgical procedure.[18,34]

Consistent with an earlier phase 1/2a study (NCT01287936) of SB623 cells for the treatment of chronic ischemic stroke,[18] there were no apparent relationships between anti-SB623 HLA antibodies and cell dose, serious adverse events, or efficacy end points in the STEMTRA trial, demonstrating the low immunoreactive potential of allogeneic SB623 cells implanted in the brain even in the absence of immunosuppressive agents.

The STEMTRA trial is the world's first double-blind, randomized, surgical sham-controlled cell implantation therapy study for treatment of chronic motor deficits secondary to TBI. As yet, there are insufficient data to define precisely the optimal implantation site of SB623 cells in relation to the site of TBI injury, which may be diffuse in nature. As a result, SB623 cell implantation sites were determined by the surgeon's judgment, which reflected real-world practice but may have caused variability of participant responses. Variability of participant responses may have also been caused by the wide participant age range, incidence of comorbidities, differences in external environmental factors, and variability of postsurgery physical therapy. Moreover, despite the STEMTRA trial being surgically sham-controlled, improvement of outcome measures may have been caused by surgical manipulation of peri-injured tissue instead of the effects of implanted SB623 cells. The authors note that, although this study was conducted across a total of 27 sites in the United States, Japan, and Ukraine, most participants were White (68.9%), with a minority of Asian participants (29.5%) and a single Black participant (1.6%).

We report a post hoc analysis of the completed 1-year, double-blind, randomized, surgical sham-controlled, phase 2 STEMTRA trial (NCT02416492). SB623-treated participants experienced higher scores and faster paced improvement on the primary efficacy end point of the FMMS score compared with control participants at 24 weeks, with sustained improvement at 48 weeks. Improvement of function and ADL scores trended to be greater in SB623-treated participants compared with control participants at 48 weeks. Implantation of SB623 cells was safe. Future clinical development should focus on the 5×10^6 SB623 cell dose because the motor score change from baseline was significantly higher than in control at both 24 weeks and 48 weeks, particularly as improvement of motor status may have relevance to improved quality of life.

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D.O. Okonkwo, P. McAllister, A.S. Achrol, and Y. Karasawa report no disclosures. M. Kawabori serves as a consultant for SanBio Inc. S.C. Cramer serves as a consultant for Constant Therapeutics, BrainQ, Myomo, MicroTransponder, Panaxium, Elevian, Stream Biomedical, NeuroTrauma Sciences, and TRCare, and previously served as a consultant for SanBio, Inc. A. Lai and S. Kesari report no disclosures. B.M. Frishberg serves as an expert witness for traumatic brain injury. L.I. Groysman reports no disclosures. A.S. Kim received grants from SanBio Inc. to support an Internet participant recruitment registry that was utilized for the submitted work, receives grants from NIH/NCATS, NIH/National Institute of Neurological Disorders and Stroke, PCORI, and AHA that are outside of the submitted work, and receives financial support as an associate editor for NEJM Journal Watch: Neurology that is outside of the submitted work. N.E. Schwartz, J.W. Chen, H. Imai, and T. Yasuhara report no disclosures. D. Chida is an employee of SanBio Inc. B. Nejadnik is a former employee of and currently serves as a consultant for SanBio Inc. D. Bates is a former employee of and previously served as a consultant for SanBio Inc. A.H. Stonehouse serves as a consultant for SanBio Inc. R.M. Richardson previously served as a consultant for SanBio Inc. G.K. Steinberg serves as a consultant for SanBio Inc., Zeiss, and Surgical Theater, and receives royalties from Peter Lazic, US. E.C. Poggio serves as a consultant for SanBio Inc. A.H. Weintraub is the owner of Neurotrauma Rehabilitation Associates LLC, Littleton, CO; serves as a contracted Medical Director for Paradigm Corporation, previously served as a contract research scientist for the Craig Hospital, Englewood, CO (2020–2022); previously served as an employee and shareholder for the CNS Medical Group, Englewood, CO (1986–2020); previously served as a consultant for SanBio Inc., and receives fees for periodic forensic medical legal consultations. Go to Neurology.org/N for full disclosures.

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Continued

Appendix *(continued)*

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