Clinical Outcomes of Transplanted Modified Bone Marrow–Derived Mesenchymal Stem Cells in Stroke
A Phase 1/2a Study

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Background and Purpose—Preclinical data suggest that cell-based therapies have the potential to improve stroke outcomes. Methods—Eighteen patients with stable, chronic stroke were enrolled in a 2-year, open-label, single-arm study to evaluate the safety and clinical outcomes of surgical transplantation of modified bone marrow–derived mesenchymal stem cells (SB623).

Results—All patients in the safety population (N=18) experienced at least 1 treatment-emergent adverse event. Six patients experienced 6 serious treatment-emergent adverse events; 2 were probably or definitely related to surgical procedure; none were related to cell treatment. All serious treatment-emergent adverse events resolved without sequelae. There were no dose-limiting toxicities or deaths. Sixteen patients completed 12 months of follow-up at the time of this analysis. Significant improvement from baseline (mean) was reported for: (1) European Stroke Scale: mean increase 6.88 (95% confidence interval, 3.5–10.3; \( P < 0.001 \)), (2) National Institutes of Health Stroke Scale: mean decrease 2.00 (95% confidence interval, −2.7 to −1.3; \( P < 0.001 \)), (3) Fugl-Meyer total score: mean increase 19.20 (95% confidence interval, 11.4–27.0; \( P < 0.001 \)), and (4) Fugl-Meyer motor function total score: mean increase 11.40 (95% confidence interval, 4.6–18.2; \( P < 0.001 \)). No changes were observed in modified Rankin Scale. The area of magnetic resonance T2 fluid-attenuated inversion recovery signal change in the ipsilateral cortex 1 week after implantation significantly correlated with clinical improvement at 12 months (\( P < 0.001 \) for European Stroke Scale).

Conclusions—In this interim report, SB623 cells were safe and associated with improvement in clinical outcome end points at 12 months.

Clinical Trial Registration—URL: https://www.clinicaltrials.gov. Unique identifier: NCT01287936. (Stroke. 2016;47:1817-1824. DOI: 10.1161/STROKEAHA.116.012995.)

Key Words: autologous transplantation ■ mesenchymal stromal cells ■ Notch 1 ■ phase 1 clinical trial ■ stem cells ■ stereotactic techniques ■ stroke

Stroke is a leading cause of long-term disability. Although an estimated 80% of patients survive for 1 year after stroke, >70% have enduring disabilities.\(^1\) There are no proven medical or surgical neuroreconstructive treatments for chronic stroke; however, the regenerative effects of different cell types and various routes of delivery are being investigated as potential treatment.\(^3,4\) To date, pilot clinical trials have reported an acceptable safety profile with some functional benefits to patients with stroke using transplanted neuronal cells differentiated from a teratocarcinoma cell line,\(^5\) human immuno- neural and hematopoietic cells,\(^6\) autologous human bone marrow–derived mononuclear cells, and mesenchymal stem cells.\(^7\) The cells used in these pilot clinical trials were administered to patients by intracerebral, intra-arterial, intravenous, or intracerebroventricular routes during the period of days to years after stroke.\(^7\)
Interim data from the PISCES Phase 1 trial for chronic stroke showed that intracerebral implantation of modified human neural stem cells was safe and seemed to be associated with improvements of neurological function in some of the stroke scales; these data were considered sufficient to warrant initiating a Phase 2 trial (PISCES II). In addition, a Phase 2 trial for subacute stroke reported that intravenous infusion of bone marrow–derived mononuclear cells was safe but had no effect on measures of neurological function.

A recent meta-analysis of preclinical studies showed that mesenchymal stem cells used to treat ischemic stroke were associated with improvements of neurological function and that the intracerebral route was associated with the greatest improvement. A Cochrane Database review of the safety and efficacy of transplanted stem cells in patients with ischemic stroke identified a single small randomized clinical trial which reported no cell-related adverse events (AEs) associated with nonstatistically significant improvements in patients after longer follow-up. The stereotactic implantation of modified bone marrow–derived mesenchymal stem cells (SB623) transiently transfected with the human Notch-1 intracellular domain is an additional option. Preclinical studies using a model of ischemic stroke in which rodent and human SB623 cells were stereotactically implanted into the striatum of the rat showed improvements in locomotor and neurological function that were associated with a reduction in peri-infarct cell loss. Other preclinical studies have reported that SB623 cells are associated with the promotion of neuronal stem cell migration and differentiation and production of extracellular matrix factors that provide trophic support for damaged cells.

This report presents preliminary 12-month interim data from a 2-year, open-label, single-arm study (NCT01287936) that was designed to evaluate the safety and clinical outcomes of the stereotactic placement of SB623 cells at the margin of the stroke in patients with chronic motor deficits >6 months after their initial stroke.

Methods

Patients

We screened 379 patients and enrolled 18 patients (mean age of 61 years; 61% female; Table I in the online-only Data Supplement). Patients did not receive poststroke rehabilitation services during the study. This study was conducted at 2 sites in the United States (Stanford University School of Medicine/Stanford Healthcare and University of Pittsburgh Medical Center), with patients being enrolled between September 2011 and August 2013. Clinical study protocols were reviewed and approved by institutional review boards, and patients provided written informed consent. Study inclusion and exclusion criteria are listed in Table I in the online-only Data Supplement.

The intent-to-treat population (n=18) that was used for the clinical evaluation included all patients enrolled in the study; at the time of this interim analysis, 16 subjects had 12-month data (2 patients had withdrawn, both were lost to follow-up [last contact with patients being at the month 3 and month 6 visits, respectively, with the second patient declining her year 1 and year 2 visits because she had moved to Taiwan]). The safety population consisted of 18 patients who enrolled in the study, received cell treatment, and had postbaseline data. Patients enrolled in the study were assessed for acute and long-term outcomes using the following measures: (1) European Stroke Scale (ESS, the primary outcome end point was ESS at 6 months); (2) NIHSS; (3) modified Rankin Scale (mRS); and (4) Fugl-Meyer (F-M) score. ESS, NIHSS, and mRS evaluations were conducted by neurologists, whereas F-M scores were evaluated by physical therapists at the 2 sites. The neurologists were not blinded to SB623 cell dose (they had access to all records) but stated that they were not aware of the dose delivered when conducting evaluations. The study visit schedule is listed in the Methods section in the online-only Data Supplement.

SB623 Cells

SB623 cells are modified bone marrow–derived mesenchymal stem cells that were developed as an allogeneic cell therapy for chronic motor deficit because of stable stroke. SB623 cells are generated under good manufacturing practices by transient transfection with a plasmid containing the human Notch-1 intracellular domain. The transfection is considered to be transient because expansion and passing of the cells result in the rapid loss of the transfected plasmid. Using an intracerebral xenograft in stroke and nonstroke rodent models, the SB623 cells only survive 1 month post implantation.

Study Design, Dosing, and Administration

Patients were divided into 3 cohorts of 6 patients. The 3 cohorts received single doses of 2.5×10⁶, 5.0×10⁶, or 10×10⁶ SB623 cells. The SB623 cells were implanted using magnetic resonance imaging stereotactic technique to define the target sites surrounding the residual stroke volume. At baseline, the mean poststroke interval was 22 months and mean stroke volume was 42 cm³. Using a single burr-hole craniostomy and 3 cannula tracks, five 20 µL cell deposits were made at 5 to 6 mm intervals along each track in the peri-infarct area. The concentration of cells ranged from 8000 to 33,000 SB623 cells per microliter. Cells were deposited at a rate not exceeding 10 µL per minute, equating to ~15 minutes for each needle track. A 0.9-mm outer diameter stereotactic cannula was used for cell injection.

Safety

A treatment-emergent AE (TEAE) was defined as any event not present before the initiation of treatment or any event already present that worsened in either intensity or frequency after exposure to study treatment. All AEs were reported according to standard procedures and were classified by investigators as being: (1) mild, (2) moderate, (3) severe, or (4) life threatening. The parameters used by investigators to evaluate the relationship of the AE to the cell treatment or study procedure are listed in Table II in the online-only Data Supplement.

Statistics

Descriptive statistics were calculated for continuous variables that included patient number, mean, SD, SEM (95% confidence interval) [CI]=±1.96×SEM], median, minimum, maximum, and 95% CIs. Descriptive statistics were calculated for categorical variables, which included the number and percentage of patients in each category. For prospectively specified end points, Wilcoxon signed-rank test was used to evaluate significance of change versus baseline for clinical outcomes, with P<0.05 considered to be statistically significant. In post hoc analyses, Pearson correlations were used to evaluate the associations between: (1) area of transient postimplantation magnetic resonance (MR) fluid-attenuated inversion recovery (FLAIR) signal intensity changes and clinical outcomes and (2) number of contrast-enhancing areas and changes in clinical outcomes. P<0.05 was considered to be statistically significant. Data analyses were performed using Statistical Analysis System (SAS) version 9.2 (Cary, NC).
Table 1. Baseline Demographics (Intent to Treat Population)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61.3 (10.29)</td>
</tr>
<tr>
<td>Median</td>
<td>64.0</td>
</tr>
<tr>
<td>Range: min–max</td>
<td>33–75</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7 (38.9)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (61.1)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>12 (66.7)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Asian</td>
<td>5 (27.8)</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>American Indian or Alaska native</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>18 (100.0)</td>
</tr>
<tr>
<td>Mean time (range) post stroke (months)</td>
<td>22.0 (7–36)</td>
</tr>
<tr>
<td>Mean size (range) of infarct (cm³)</td>
<td>42.3 (1.0–87.0)</td>
</tr>
<tr>
<td>Baseline measures of clinical outcome end points (SD; 95% CI)</td>
<td></td>
</tr>
<tr>
<td>ESS</td>
<td>58.44 (6.27; 55.3–61.6)</td>
</tr>
<tr>
<td>NIHSS</td>
<td>9.44 (1.89; 8.5–10.4)</td>
</tr>
<tr>
<td>mRS</td>
<td>3.22 (0.43; 3.0–3.4)</td>
</tr>
<tr>
<td>F-M total score</td>
<td>133.61 (20.90; 123.2–144.0)</td>
</tr>
<tr>
<td>F-M motor function total score</td>
<td>30.44 (15.14; 22.9–38.0)</td>
</tr>
</tbody>
</table>

Cl indicates confidence interval; ESS, European Stroke Scale; F-M, Fugl-Meyer; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

Results

Safety Evaluations

In this analysis, all patients experienced at least 1 TEAE in the 12 months after implantation of SB623 cells (Table 2). The most frequently reported TEAEs (percent of patients) in the pooled dose assessment of SB623 cells were headache related to surgical procedure (77.8%), nausea (33.3%), vomiting (22.2%), depression (22.2%), muscle spasticity (22.2%), fatigue (16.7%), blood glucose increase (16.7%), and C-reactive protein increase (16.7%; Table 2). There was no relation between cell dose levels and frequency of TEAEs.

In the safety population (N=18), patients experienced a total of 28 treatment-related TEAEs during 12 months of follow-up. In total, 88.9% of patients (16 TEAEs in 18 patients) experienced a TEAE that investigators evaluated as being unrelated to cell treatment (Table III in the online-only Data Supplement). In comparison, 44.4% (8 TEAEs in 18 patients) experienced a TEAE that was unlikely to be related to the cells and 22.2% (4 TEAEs in 18 patients) experienced a TEAE that was possibly related (Table III in the online-only Data Supplement). No patients experienced a TEAE that was probably or definitely related to cell treatment. The 4 TEAEs (22.2%) that were possibly related to the cells were muscle spasticity (2), gait disturbance (1), and procedural headache (1).

More patients possibly, probably, or definitely experienced TEAEs related to the surgical procedure than to the cells (Table III in the online-only Data Supplement). Post-surgery headache was the most common TEAE that was probably or definitely related to the procedure, experienced by 77.8% (14 in 18 patients) of patients (Table III in the online-only Data Supplement).

There were 6 serious TEAEs experienced by 6 patients, with no clear trends regarding serious TEAEs and cell dosage (Table 3). Serious TEAEs were unrelated or unlikely to be related to cell treatment; however, a single patient developed an asymptomatic subdural fluid collection that was definitely related to the procedure and was managed by burr-hole drainage. An additional patient had a seizure on study day 70, which the investigator evaluated as life threatening and probably related to the surgical procedure. A patient underwent stenting for an asymptomatic cervical carotid artery stenosis on study day 291; the investigator evaluated the event as being unrelated to both cell treatment and surgical procedure.

A patient experienced a transient ischemic attack on study day 334 that was associated with worsening facial droop and slurred speech. Although the transient ischemic attack was assessed as being in the same brain area as the original stroke and SB623 cell delivery, it occurred 11 months after surgery and was evaluated by the investigator as being unrelated to both cell treatment and surgical procedure. All serious TEAEs received supportive therapy and were evaluated as being recovered or resolved without sequelae (Table 3).

We found no clinically meaningful changes in hematology parameters, biochemistry parameters, lipids, cytokines (tumor necrosis factor-α, interleukin-6, and interferon-γ), or vital signs during this 12-month analysis. In addition, no antibody-related sensitization to SB623 cells was observed.

Clinical Outcome Evaluations

Clinical outcome analyses were conducted on 16 patients who had completed 12 months of treatment in the intent-to-treat population (n=18). The baseline mean (SD) ESS total score was 58.44 (6.27). The mean ESS total score increased significantly from baseline by 2.00 (95% CI, −2.7 to −1.3; P<0.001) at 12 months and was increased significantly from baseline at all other time points, starting at 1 month (Figure 1A).

Significant improvements from baseline of the NIHSS total score was also observed at all time points starting with 1 month. The baseline mean (SD) NIHSS total score was 9.44 (1.89). The mean NIHSS total score decreased from baseline by 2.00 (95% CI, −2.7 to −1.3; P<0.001) at 12 months, representing a measurable improvement (Figure 1B).

The F-M total score and F-M motor function total score of the baseline means (SDs) were 133.61 (20.90) and 30.44
The mean F-M total score increased significantly from baseline by 19.20 (95% CI, 11.4–27.0; *P* <0.001) at 12 months (Figure 1C), and the mean F-M motor function total score increased significantly from baseline by 11.40 (95% CI, 4.6–18.2; *P* <0.001) at 12 months (Figure 1D).

Both F-M total score and F-M motor function total score were significantly increased from baseline at all time points (Figure 1C and 1D). From a baseline mean (SD) score of 3.22 (0.43), no change was seen in mRS at 12 months (0.00; 95% CI, −0.2 to 0.2; *P*=1.0000). Correlation of improvements of clinical outcome end points with cell dose levels did not show any clear dose–response relationships. There was no association between improvement in clinical outcome measures and either baseline stroke severity or baseline patient age.

<table>
<thead>
<tr>
<th>System Organ Class Preferred Term, n (%)</th>
<th>2.5×10⁶ Cells, n=6</th>
<th>5.0×10⁶ Cells, n=6</th>
<th>10×10⁶ Cells, n=6</th>
<th>Pooled Cells, N=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE*</td>
<td>6 (100.0)</td>
<td>6 (100.0)</td>
<td>6 (100.0)</td>
<td>18 (100.0)</td>
</tr>
<tr>
<td>Headache/procedural headache†</td>
<td>6 (100.0)</td>
<td>4 (66.7)</td>
<td>4 (66.7)</td>
<td>14 (77.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0.0)</td>
<td>3 (50.0)</td>
<td>3 (50.0)</td>
<td>6 (33.3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0.0)</td>
<td>2 (33.3)</td>
<td>2 (33.3)</td>
<td>4 (22.2)</td>
</tr>
<tr>
<td>Depression</td>
<td>0 (0.0)</td>
<td>2 (33.3)</td>
<td>2 (33.3)</td>
<td>4 (22.2)</td>
</tr>
<tr>
<td>Muscle spasticity</td>
<td>2 (33.3)</td>
<td>1 (16.7)</td>
<td>1 (16.7)</td>
<td>4 (22.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0 (0.0)</td>
<td>1 (16.7)</td>
<td>2 (33.3)</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>Blood glucose increased</td>
<td>2 (33.3)</td>
<td>1 (16.7)</td>
<td>0 (0.0)</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>C-reactive protein increased</td>
<td>1 (16.7)</td>
<td>1 (16.7)</td>
<td>1 (16.7)</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>Convulsion</td>
<td>1 (16.7)</td>
<td>1 (16.7)</td>
<td>0 (0.0)</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (16.7)</td>
<td>1 (16.7)</td>
<td>0 (0.0)</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Pneumocephalus</td>
<td>0 (0.0)</td>
<td>2 (33.3)</td>
<td>0 (0.0)</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Subdural hematoma</td>
<td>0 (0.0)</td>
<td>2 (33.3)</td>
<td>0 (0.0)</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>0 (0.0)</td>
<td>1 (16.7)</td>
<td>1 (16.7)</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 (0.0)</td>
<td>1 (16.7)</td>
<td>1 (16.7)</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2 (33.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>1 (16.7)</td>
<td>1 (16.7)</td>
<td>0 (0.0)</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>1 (16.7)</td>
<td>1 (16.7)</td>
<td>0 (0.0)</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (33.3)</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1 (16.7)</td>
<td>0 (0.0)</td>
<td>1 (16.7)</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>0 (0.0)</td>
<td>2 (33.3)</td>
<td>0 (0.0)</td>
<td>2 (11.1)</td>
</tr>
</tbody>
</table>

TEAE indicates treatment-emergent adverse event.
*A TEAE is defined as any event not present before the initiation of treatment or any event already present that worsened in either intensity or frequency after exposure to study treatment.
†Headache/procedural headache: because of reporting verbatim differences, headaches were coded into 2 terms.

<table>
<thead>
<tr>
<th>Cell Dose</th>
<th>Serious Adverse Event</th>
<th>Relationship to Cell Treatment</th>
<th>Relationship to Procedure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5×10⁶</td>
<td>Seizure</td>
<td>Unrelated</td>
<td>Probably</td>
<td>Recovered/resolved</td>
</tr>
<tr>
<td>2.5×10⁶</td>
<td>Stenting of asymptomatic carotid artery stenosis</td>
<td>Unrelated</td>
<td>Unrelated</td>
<td>Recovered/resolved</td>
</tr>
<tr>
<td>5.0×10⁶</td>
<td>Asymptomatic subdural hematoma/hyroma</td>
<td>Unrelated</td>
<td>Definitely</td>
<td>Recovered/resolved</td>
</tr>
<tr>
<td>5.0×10⁶</td>
<td>Transient ischemic attack</td>
<td>Unrelated</td>
<td>Unrelated</td>
<td>Recovered/resolved</td>
</tr>
<tr>
<td>10×10⁶</td>
<td>Urinary tract infection/sepsis</td>
<td>Unrelated</td>
<td>Unrelated</td>
<td>Recovered/resolved</td>
</tr>
<tr>
<td>10×10⁶</td>
<td>Pneumonia</td>
<td>Unlikely</td>
<td>Possibly</td>
<td>Recovered/resolved</td>
</tr>
</tbody>
</table>
MR Findings

Thirteen of the 18 patients in the trial demonstrated new signal changes on MR T2 FLAIR imaging (0.5–9.2 cm²; 0.6–3.5 cm maximum diameter) primarily in or adjacent to the premotor cortex along the cannula track at 1 week post-transplantation (except 1 patient without a week 1 MR who showed a new FLAIR signal at 2 weeks). These FLAIR signal changes were diffusion-weighted image negative, were not present on the day 1 post-transplant MR scan, and were found to have resolved on the month 1 or 2 post-transplant MR scan (Figure 2). There were significant Pearson correlations between the size of the initial post-transplant FLAIR signal changes and neurological recovery as measured by change from baseline in clinical outcomes at 12 months (ESS total score: 0.818, P<0.001; NIHSS total score: −0.688, P<0.01; F-M total score: 0.708, P<0.01; F-M motor function total score: 0.668, P<0.01).

We also examined the relationship between FLAIR signal changes and ≥10% change in the F-M motor function total score, a change that is accepted as a clinically meaningful improvement in chronic stroke.26–29 At 12 months, the positive predictive value of whether a FLAIR signal change would determine a clinically meaningful improvement was seen in 6 of 12 cases, whereas the negative predictive value (ie, the absence of a FLAIR signal change) of predicting a nonclinically meaningful improvement was seen in 3 of 4 cases.

Contrast-enhancing areas in the cannula tract were observed at 1 week post-transplant in 15 patients (except 1 patient without a week 1 MR who showed contrast enhancement at 2 weeks), 12 of whom had FLAIR signal changes. Such changes resolved with the same time course as the FLAIR signal abnormalities. There were significant Pearson correlations between the number of contrast-enhancing areas and change from baseline in measures of neurological recovery at 12 months (ESS total score: 0.904, P<0.001; NIHSS total score: −0.643, P<0.05; F-M total score: 0.798, P<0.01; F-M motor function total score: 0.728, P<0.01).

Figure 1. A–D, Change of clinical outcome end points from baseline for pooled SB623 cells at 12 months (intent-to-treat population, n=18). (A) European Stroke Scale. (B) National Institutes of Health Stroke Scale. (C) Fugl-Meyer (F-M) total score. (D) F-M motor function total score. Error bars represent SEM. P values represent significance of change vs baseline using the Wilcoxon signed-rank test (P<0.05), which were not corrected for multiplicity.
Discussion

Despite stroke representing a major cause of mortality and severe disability, the only proven therapies for ischemic stroke are intravenous tissue-type plasminogen activator and intra-arterial thrombectomy, both of which must be administered within a few hours of stroke onset.3,4,30,31 Currently, there are no proven medical or surgical neurorestorative treatments available for subacute or chronic stroke. However, stem cell and cultured cell therapy for chronic stroke is moving quickly into the clinical arena.3,6 For example, the stereotactic implantation of cultured human neuronal cells into the brains of patients with stroke was investigated in Phase 1 and 2 studies which showed that although the surgical procedure and cell treatment were safe, there was no significant improvement in motor function, despite measureable improvements in some patients.5,16

Assessment of Potential Benefit

This is the first reported intracerebral stem cell transplant study for stroke in North America, in which stereotactic implantation of SB623 cells was generally safe and well tolerated by patients with most TEAEs being of moderate intensity. No TEAEs were evaluated as being probably or definitely related to cell treatment; however, consistent with an earlier study that also used stereotactic intracranial administration of cells, many TEAEs were probably or definitely related to the surgical procedure.5 Of 6 serious AEs (all of which resolved without sequelae), 2 were probably or definitely related to the surgical procedure. Overall in this study, there were no clear dose responses to measures of safety.

The neurological deficits of patients with chronic stroke were assessed using standard impairment scales, specifically the ESS, NIHSS, and F-M scale. Despite these patients having chronic stroke and stable neurological function scores at baseline, there were significant improvements in the mean scale scores of ESS, NIHSS, F-M total score, and F-M motor function total score at 12 months after treatment. The primary clinical outcome measure (significant improvement in ESS at 6 months) was also positive.

The F-M motor function total score is well established as a reliable and valid method of assessing recovery from chronic stroke.24,32,33 A ≥10-point improvement (ie, ≥10% of the 100-point scale range) in the F-M motor function total score is accepted as a clinically meaningful change in chronic stroke.26–29 In this study, the mean F-M motor function total score increased from baseline by 11.4 points, representing a clinically meaningful improvement at 12 months. Furthermore, a total of 7 patients experienced a ≥10-point change from baseline of the F-M motor function total score. For patients in the study, this represented a clinical improvement in the power of upper and lower limbs, ranging from an improvement in the ability to stand to the disappearance of tremor.

The mRS has typically been applied to measure long-term outcomes in global neurological function after acute stroke34; however, the value of the mRS to measure outcomes in patients with chronic stroke has not been established.35 In this study, patients did not experience a significant improvement in mRS at 12 months or at any time point after treatment. Considering these factors, it is not surprising that we were unable to detect significant change in the mRS during 12 months. The mRS has typically been applied to measure long-term outcomes in global neurological function after acute stroke34; however, the value of the mRS to measure outcomes in patients with chronic stroke has not been established.35 In this study, patients did not experience a significant improvement in mRS at 12 months or at any time point after treatment. Considering these factors, it is not surprising that we were unable to detect significant change in the mRS during 12 months. The most dramatic recovery in motor function after stroke is reported to occur in the first 30 days after stroke, with improvements in motor function reaching a plateau at 6 months regardless of stroke severity.36–38 In addition, patients treated with cultured human neuronal cells in earlier clinical trials were also considered to have stable chronic stroke after 6 months.5,16 It is significant that patients enrolled in this study...
had a minimum poststroke time of 6 months at baseline (mean poststroke time of 22 months) and were therefore already in a chronic stroke setting.

Survival of SB623 Cells
The transfection with Notch-1 in SB623 cells is temporary but results in altered patterns of DNA methylation and protein expression.12 In preclinical studies, SB623 cells: (1) secrete factors that protect cells from hypoxic injury, (2) secrete trophic factors that support damaged cells, (3) secrete extracellular matrix proteins that support neural cell growth, (4) have anti-inflammatory effects, (5) have immunosuppressive effects, (6) promote angiogenesis, (7) promote neuronal stem cell migration and differentiation, and (8) provide a biobridge of extracellular matrix metalloproteinases.14,15,25,39,40 Because transplanted human SB623 cells only survive for 1 month in preclinical stroke and nonstroke models,15,28 persistent neurological recovery may be achieved by the secretion of supportive molecules rather than by the integration of transplanted stem cells.

Potential Relevance of Postimplant Imaging Changes
The positive correlation between the area of post-transplant MR T2 FLAIR signal changes, which appeared at 1 week and resolved by 1 to 2 months, and measures of neurological recovery at 12 months is interesting. The pathogenesis of the FLAIR signal changes is unknown, but diffusion-weighted image negative and therefore not representative of cytotoxic edema (ie, an acute infarct). Despite resolution of FLAIR signal changes by 1 to 2 months, the neurological recovery documented on several outcome scales was sustained for at least 12 months. The observation that the transplanted cells likely do not persist for >1 month in preclinical models suggests that the acute cell transplantation stimulates a sustained recovery process. Several patients without post-transplant FLAIR signal changes showed some neurological recovery, although only 1 of the FLAIR-negative patients demonstrated a clinically meaningful improvement at 12 months. The significance of the MR findings is uncertain considering the small number of patients, but given the association with clinical improvement, it deserves further examination in subsequent studies.

Study Limitations
This study is a small-scale, open-label, dose-escalation, Phase 1/2a trial and is therefore limited by its nonrandomized, uncontrolled design and small number of patients. In addition, the patient screening process was highly selective, with only 4.7% of all screened patients enrolled in the trial. Therefore, the application of conclusions from this early phase trial to the general chronic stroke population should be performed with caution. The definition of stable chronic stroke used at baseline in this trial (ie, 2 NIHSS evaluations conducted within 3 weeks of enrollment with no score change of greater than ±1 point) has also been used in previous trials. However, other studies have defined chronic stable stroke by use of minimum changes in several stroke scales during 6 weeks. Therefore, differences in the definition of chronic stable stroke should be considered while interpreting conclusions from this trial.

The positive measures of safety and clinical outcomes reported here highlight the need for large-scale Phase 2b and 3 clinical trials to further evaluate the use of SB623 cells for the treatment of chronic stroke.

Conclusions
In this interim analysis of the first intracerebral stem cell transplant study for stroke in North America, treatment with SB623 cells was generally safe and well tolerated and demonstrated a significant improvement in neurological function after 12 months.

Acknowledgments
Dr Anthony Stonehouse provided medical writing support. He is an employee of Watson & Stonehouse Enterprises, LLC, and was funded by SanBio, Inc.

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SanBio, Inc funded the study development, data collection, and analysis. The authors are responsible for data interpretation, article content, and the decision to submit the article for publication.

Disclosures
This study was partly conducted at Stanford University School of Medicine and Stanford Health Care and was funded by a contract with SanBio, Inc, which provided principal investigator, coinvestigator, and coordinator fees. Drs Steinberg and Schwartz and M.L. Coburn are Stanford University School of Medicine employees. Dr Steinberg is a member of the Medtronic Neuroscience Strategic Advisory Board and a consultant for Qool Therapeutics and for Peter Lazic US, Inc. This study was partly conducted at the University of Pittsburgh Medical School and University of Pittsburgh Medical Center (UPMC) and was funded by a contract with SanBio, Inc, which provided principal investigator and coordinator fees. Drs Wechsler and Lunsford are employees of the University of Pittsburgh Medical School and University of Pittsburgh Medical Center. J.B. Billigen is an employee of UPMC. Dr Kondziolka is a former employee of UPMC and was a consultant for Elekta AB. Dr Wechsler is a stockholder in Silk Road Medical and Remedy Pharm and receives unrelated grant funding from Athersys, Inc. Dr Lunsford is a consultant for and stockholder of Elekta AB. Personnel support for a principal investigator in this study was provided by the University of California, San Francisco, and was funded by a contract with SanBio, Inc. Dr Kim is an employee of the University of California, San Francisco. He receives unrelated grant funding from BioGen Idec. Drs Bates and McGrogan are full-time employees of SanBio, Inc. B. King was paid consultancy fees from SanBio, Inc. Drs Case and Yankee are former employees and current stockholders of SanBio, Inc. Dr Yankee is a consultant for SanBio, Inc. Dr McGrogan is a stockholder of SanBio, Inc. Drs Steinberg, Kondziolka, Schwartz, Wechsler, Lunsford, Kim, Bates, Case, McGrogan, and Yankee and M.L. Coburn, J.B. Billigen, and B. King disclose no other financial or personal relationships that could influence the conduct or reporting of this study. Dr Johnson discloses no other financial or personal relationships that could influence the conduct or reporting of this study.

References


Clinical Outcomes of Transplanted Modified Bone Marrow–Derived Mesenchymal Stem Cells in Stroke: A Phase 1/2a Study


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SUPPLEMENTAL MATERIAL

Clinical Outcomes of Transplanted Modified Bone Marrow-Derived Mesenchymal Stem Cells in Stroke: A Phase 1/2a Study

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7Western Statistical Consulting, LLC, 530 E. McDowell Road #107-284, Phoenix, AZ 85004
SUPPLEMENTARY METHODS

Study Visit Schedule

Patients attended the following visit schedule: Screen 1 (Study Week: -3); Screen 2 (Study Week: -1); Baseline (Study Day: -2 to -1); Enrollment (Study Day: -1 to 1); Surgical Procedure (Day 1); Visits (Days 2, 8; Months 1, 2, 3, 4, 6, 9, and 12); Final Visit (Month 24). Stroke scales including ESS, NIHSS, mRS, and F-M were performed at each visit. Brain magnetic resonance (MR) imaging scans were conducted at Screen 1 (Study Week: -3); Baseline (Study Day -2 to -1); Visits (Days 1, 2, 8; Months 1, 2, 3, 4, 6, 9, 12, 24).
### Supplementary Table I. Study Inclusion and Exclusion Criteria

#### Inclusion Criteria
- Aged 18-75 years.
- Documented history of completed ischemic stroke in the subcortical region of the middle cerebral artery or lenticulostriate artery with or without cortical involvement, with findings correlated preferably by magnetic resonance imaging (MRI) or by computed tomography (CT) scan if MRI was contraindicated.
- Between 6 and 60 months post-stroke, and had a motor neurological deficit.
- No significant further improvement with physical therapy/rehabilitation (confirmed by no change in NIHSS greater than ±1 within 3 weeks prior to enrollment).
- Had 2 evaluations during the prior 3 weeks with no more than ±1 point change in clinical evaluation using the NIHSS.
- NIHSS score of >7.
- mRS of 3-4.
- Able and willing to undergo MRI, CT, and positron emission tomography (PET) scans of the head.
- Agreed to the use of anti-platelet, anti-coagulant, or non-steroidal anti-inflammatory (NSAID) drugs to be determined by the local medical staff in accordance with the American College of Chest Physicians 2012 guideline if applicable, provided that no anti-platelet, anti-coagulant, or NSAID drugs were to be restarted after surgery until determined to be safe following MRI scan of the head on Day 8.
- Normal emotional status; i.e., no disabling psychological deficits.
- Patient or legal authorized representative was able to understand and sign an informed consent form.
- Uncontrolled psychiatric illness, including depression (Hamilton Score >14).
- A total bilirubin level of >1.5 mg/dL.
- A serum creatinine level of >1.5 mg/dL.
- A hemoglobin level of <10.0 g/dL.
- An absolute neutrophil count of <2,000/mm³.
- A lymphocyte count of <800/mm³.
- A platelet count of <100,000/mm³.
- Had liver disease supported by aspartate aminotransferase or alanine aminotransferase of ≥2.5x institutional upper limit of normal.
- A serum calcium level of >11.5 mg/dL.
- Had an International Normalized Ratio of Prothrombin Time (INR) of >1.2.
- Signs and symptoms of intracranial herniation or increased intracranial pressure.
- Acute intracranial hemorrhage.
- Used neuroleptic drugs.
- Unexplained abnormal preoperative test values (blood tests, electrocardiogram [ECG], chest X-ray); patients with ECG evidence to suggest a recent myocardial infarction, major dysrhythmia, atrial fibrillation, congestive heart failure, or x-ray evidence of infection were excluded.
- Participated in any other investigational trial within 4 weeks of initial screening and within 7 weeks of study entry.
- Botulinum toxin injection, phenol injection, intrathecal baclofen, or any other interventional treatments for spasticity (except bracing and splinting) within the previous 3 months.
- Ongoing use of herbal or other non-traditional drugs.
- Ongoing drug or alcohol abuse.
- Contraindications to MRI, CT, or PET scans of the head.
- Pregnant or lactating.
- History of >1 symptomatic stroke.
- Presence or history of any other major neurological disease.
- Cerebral infarct size >100 cm³ measured by MRI scan.
- Myocardial infarction in the past 6 months.
- Known malignancy except squamous or basal cell carcinoma of the skin.
- History of central nervous system malignancy.
- History of seizures or current use of antiepileptic medication.
- Uncontrolled systemic illness, including but not limited to: diabetes, hypertension (systolic blood pressure: >150 mm Hg or diastolic blood pressure: >95 mm Hg), renal failure, hepatic failure, or cardiac failure.

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- Contraindications to MRI, CT, or PET scans of the head.
- Pregnant or lactating.
- History of >1 symptomatic stroke.
- Presence or history of any other major neurological disease.
Supplementary Table II. Relationship of Adverse Events to Administration of Cell Treatment/Procedure

<table>
<thead>
<tr>
<th>Description</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated</td>
<td>No temporal relationship to cell treatment/procedure, or the presence of a reasonable causal relationship between another drug, concurrent disease, or circumstance and the AE.</td>
</tr>
<tr>
<td>Unlikely</td>
<td>A temporal relationship to cell treatment/procedure, but no reasonable causal relationship between the cell treatment/procedure and the AE.</td>
</tr>
<tr>
<td>Possibly</td>
<td>A reasonable causal relationship between the cell treatment/procedure and the AE. Information related to withdrawal of cell treatment/procedure was lacking or unclear.</td>
</tr>
<tr>
<td>Probably</td>
<td>A reasonable causal relationship between the cell treatment/procedure and the AE. The event responded to withdrawal of cell treatment/procedure. Re-challenge was not required.</td>
</tr>
<tr>
<td>Definitely</td>
<td>A reasonable causal relationship between the cell treatment/procedure and the AE. The event responded to withdrawal of cell treatment/procedure, and recurred with re-challenge, when clinically feasible.</td>
</tr>
</tbody>
</table>
Supplementary Table III. Most Frequently Reported (≥3) Treatment Emergent Adverse Events Occurring by Relationship to Cell Treatment or Procedure (Safety Population)

<table>
<thead>
<tr>
<th>System Organ Class Preferred Term, n (%)</th>
<th>Relationship to Cell Treatment*</th>
<th>2.5x10⁶ Cells, n=6</th>
<th>5.0x10⁶ Cells, n=6</th>
<th>10x10⁶ Cells, n=6</th>
<th>Pooled Cells, n=18</th>
<th>Relationship to Procedure*</th>
<th>2.5x10⁶ Cells, n=6</th>
<th>5.0x10⁶ Cells, n=6</th>
<th>10x10⁶ Cells, n=6</th>
<th>Pooled Cells, n=18</th>
</tr>
</thead>
<tbody>
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<td>Any TEAE†</td>
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<td>5 (83.3)</td>
<td>6 (100.0)</td>
<td>5 (83.3)</td>
<td>16 (88.9)</td>
<td>Unrelated</td>
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<td>5 (83.3)</td>
<td>5 (83.3)</td>
<td>15 (83.3)</td>
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<td>Unlikely</td>
<td>4 (66.7)</td>
<td>1 (16.7)</td>
<td>3 (50.0)</td>
<td>8 (44.4)</td>
<td>Unrelated</td>
<td>3 (50.0)</td>
<td>0 (0.0)</td>
<td>1 (16.7)</td>
<td>4 (22.2)</td>
</tr>
<tr>
<td></td>
<td>Possibly</td>
<td>2 (33.3)</td>
<td>1 (16.7)</td>
<td>1 (16.7)</td>
<td>4 (22.2)</td>
<td>Possibly</td>
<td>2 (33.3)</td>
<td>5 (83.3)</td>
<td>3 (50.0)</td>
<td>10 (55.6)</td>
</tr>
<tr>
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<td></td>
<td>1 (16.7)</td>
<td>1 (16.7)</td>
<td>1 (16.7)</td>
<td>5 (27.8)</td>
<td>Definitely</td>
<td>3 (50.0)</td>
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<td>2 (33.3)</td>
<td>6 (33.3)</td>
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<td>0 (0.0)</td>
<td>1 (5.6)</td>
<td>Definitely</td>
<td>2 (33.3)</td>
<td>1 (16.7)</td>
<td>1 (16.7)</td>
<td>4 (22.2)</td>
</tr>
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<td>1 (16.7)</td>
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<td>2 (11.1)</td>
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<td>2 (33.3)</td>
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<td>Unrelated</td>
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<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (5.6)</td>
</tr>
</tbody>
</table>

†TEAE: treatment emergent adverse event. A TEAE is defined as any event not present prior to the initiation of treatment or any event already present that worsened in either intensity or frequency following exposure to study treatment.

*The relationship to cell treatment/procedure and TEAE was evaluated by the investigator according to the following guidance:

Unrelated: No temporal relationship to cell treatment/procedure, or the presence of a reasonable causal relationship between another drug, concurrent disease, or circumstance and the adverse event (AE).

Unlikely: A temporal relationship to cell treatment/procedure, but no reasonable causal relationship between the cell treatment/procedure and the AE.

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REFERENCES
遺伝子改変骨髄間葉系幹細胞を移植した脳卒中患者の臨床転帰
第 I/IIa 相試験
Clinical Outcomes of Transplanted Modified Bone Marrow–Derived Mesenchymal Stem Cells in Stroke
A Phase 1/2a Study
Gary K. Steinberg, MD, PhD1; Douglas Kondziolka, MD2; Lawrence R. Wechsler, MD3, et al.
1 Department of Neurosurgery, Stanford University School of Medicine and Stanford Health Care, CA; 2 Department of Neurosurgery, New York University and NYU Langone Medical Center, NY; 3 Department of Neurology, University of Pittsburgh Medical School and University of Pittsburgh Medical Center, PA

背景および目的：前臨床データでは、細胞治療で脳卒中の転帰が改善する可能性が示唆されている。方法：安定した慢性期脳卒中患者18例を2年間の非盲検単一群試験に登録し、遺伝子改変骨髄間葉系幹細胞（SB623）移植手術の安全性と臨床転帰を評価した。

結果：安全性解析集団のすべての患者（N = 18）に治療期有害事象（treatment-emergent adverse event: TEAE）が1件以上発現した。6例の患者に6件の重篤なTEAEが発現し、2件はおそらく/または明らかに外科手術に関連する事象であった。重篤なTEAEはすべて回復し、後遺症はみられなかった。用量制限毒性および死亡は確認されなかった。本解析の時点で16例が12ヶ月間の追跡調査を完了した。以下について、ベースライン（平均）からの有意な改善が報告された。（1）European Stroke Scale：平均6.88増加（95%信頼区間（CI）：3.5～10.3、P < 0.001）、（2）米国立衛生研究所脳卒中スケール（NIHSS）：平均2.00低下（95% CI：−2.7 ～ −1.3、P < 0.001）、（3）Fugl-Meyer合計スコア：平均19.20増加（95% CI：11.4 ～ 27.0、P < 0.001）、（4）Fugl-Meyer運動機能合計スコア：平均11.40増加（95% CI：4.6 ～ 18.2、P < 0.001）。変いRankin Scale（mRS）に変化はなかった。移植の1週間後に撮像した患側大脳皮質のT2 FLAIR MR画像の信号変化領域は12ヶ月後の臨床的改善と有意に相関した（European Stroke Scale、P < 0.001）。

結論：本中間報告において、SB623細胞は安全であり、12ヶ月時点の臨床転帰評価項目を改善した。

臨床試験登録情報：URL: https://www.clinicaltrials.gov. 固有の識別番号：NCT01287936。