SUPPLEMENTAL MATERIAL

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

Gary K. Steinberg, MD, PhD,[1,2]* Douglas Kondziolka, MD,[3] Lawrence R. Wechsler, MD,[4] L. Dade Lunsford, MD,[3] Maria L. Coburn, BA,[1] Julia B. Billigen, RN, BS,[4] Anthony S. Kim, MD, MAS,[5] Jeremiah N. Johnson, MD,[1] Damien Bates, MD, PhD,[6] Bill King, MS,[7] Casey Case, PhD,[6] Michael McGrogan, PhD,[6] Ernest W. Yankee, PhD,[6] Neil E. Schwartz, MD, PhD[2]

[1]Department of Neurosurgery, Stanford University School of Medicine and Stanford Health Care, 300 Pasteur Drive, Stanford, CA 94305
[2]Department of Neurology and Neurological Sciences, Stanford University School of Medicine and Stanford Health Care, 300 Pasteur Drive, Stanford, CA 94305
[3]Department of Neurosurgery, University of Pittsburgh Medical School and University of Pittsburgh Medical Center, 200 Lothrop Street, Pittsburgh, PA 15213
[4]Department of Neurology, University of Pittsburgh Medical School and University of Pittsburgh Medical Center, 3471 Fifth Avenue, Pittsburgh, PA 15213
[5]Department of Neurology, University of California, San Francisco, 675 Nelson Rising Lane, Room 411B, San Francisco, CA 94158
[6]SanBio, Inc. 231 S. Whisman Road, Mountain View, CA 94041
[7]Western 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,[1] 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.

Exclusion Criteria

- History of >1 symptomatic stroke.
- Presence or history of any other major neurological disease.
- Cerebral infarct size >100 cm^3 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.
- 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/mm^3.
- A lymphocyte count of <800/mm^3.
- A platelet count of <100,000/mm^3.
- 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.
- Female patient of childbearing potential unwilling to use an adequate birth control method during the first 6 months of the study.
- Any other condition or situation that the investigator believed may interfere with the safety of the patient or the intent and conduct of the study.
- Had the presence of serum antibodies to donor SB623 cells with a Luminex value of >1,000 Maximum Fluorescence Intensity.

Supplementary Table II. Relationship of Adverse Events to Administration of Cell Treatment/Procedure

Description	Relationship
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 AE.
Unlikely	A temporal relationship to cell treatment/procedure, but no reasonable causal relationship between the cell treatment/procedure and the AE.
Possibly	A reasonable causal relationship between the cell treatment/procedure and the AE. Information related to withdrawal of cell treatment/procedure was lacking or unclear.
Probably	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.
Definitely	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.

Supplementary Table III. Most Frequently Reported (≥3) Treatment Emergent Adverse Events Occurring by Relationship to Cell Treatment or Procedure (Safety Population)

System Organ Class Preferred Term, n (%)	Relationship to Cell Treatment*	$2.5x10^6$ Cells, n=6	$5.0x10^6$ Cells, n=6	$10x10^6$ Cells, n=6	Pooled Cells, n=18	Relationship to Procedure*	$2.5x10^6$ Cells, n=6	$5.0x10^6$ Cells, n=6	$10x10^6$ Cells, n=6	Pooled Cells, n=18
Any TEAE†	**Unrelated**	**5 (83.3)**	**6 (100.0)**	**5 (83.3)**	**16 (88.9)**	**Unrelated**	**5 (83.3)**	**5 (83.3)**	**5 (83.3)**	**15 (83.3)**
	Unlikely	**4 (66.7)**	**1 (16.7)**	**3 (50.0)**	**8 (44.4)**	**Unlikely**	**3 (50.0)**	**0 (0·0)**	**1 (16.7)**	**4 (22.2)**
	Possibly	**2 (33.3)**	**1 (16.7)**	**1 (16.7)**	**4 (22.2)**	**Possibly**	**2 (33.3)**	**5 (83.3)**	**3 (50.0)**	**10 (55.6)**
	—	—	—	—	—	**Probably**	**3 (50.0)**	**3 (50.0)**	**4 (66.7)**	**10 (55.6)**
	—	—	—	—	—	**Definitely**	**2 (33.3)**	**4 (66.7)**	**1 (16.7)**	**7 (38.9)**
Headache/Procedural headache	Unrelated	3 (50.0)	3 (50.0)	2 (33.3)	8 (44.4)	Unrelated	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Unlikely	3 (50.0)	1 (16.7)	1 (16.7)	5 (27.8)	Possibly	1 (16.7)	2 (33.3)	1 (16.7)	4 (22.2)
	Possibly	0 (0.0)	0 (0.0)	1 (16.7)	1 (5.6)	Probably	3 (50.0)	1 (16.7)	2 (33.3)	6 (33.3)
	—	—	—	—	—	Definitely	2 (33.3)	1 (16.7)	1 (16.7)	4 (22.2)
Muscle spasticity	Unrelated	1 (16.7)	0 (0.0)	1 (16.7)	2 (11.1)	Unrelated	1 (16.7)	0 (0.0)	1 (16.7)	2 (11.1)
	Possibly	1 (16.7)	1 (16.7)	0 (0.0)	2 (11.1)	Possibly	1 (16.7)	1 (16.7)	0 (0.0)	2 (11.1)
Nausea	Unrelated	0 (0.0)	2 (33.3)	2 (33.3)	4 (22.2)	Unrelated	0 (0.0)	1 (16.7)	1 (16.7)	2 (11.1)
	Unlikely	0 (0.0)	1 (16.7)	1 (16.7)	2 (11.1)	Possibly	0 (0.0)	2 (33.3)	2 (33.3)	4 (22.2)
Vomiting	Unrelated	0 (0.0)	2 (33.3)	2 (33.3)	4 (22.2)	Unrelated	0 (0.0)	1 (16.7)	1 (16.7)	2 (11.1)
	—	—	—	—	—	Possibly	0 (0.0)	1 (16.7)	1 (16.7)	2 (11.1)
Fatigue	Unrelated	0 (0.0)	1 (16.7)	2 (33.3)	3 (16.7)	Unrelated	0 (0.0)	0 (0.0)	1 (16.7)	1 (5.6)
	—	—	—	—	—	Possibly	0 (0.0)	1 (16.7)	1 (16.7)	2 (11.1)
Depression	Unrelated	0 (0.0)	2 (33.3)	2 (33.3)	4 (22.2)	Unrelated	0 (0.0)	2 (33.3)	2 (33.3)	4 (22.2)
Blood glucose increased	Unrelated	2 (33.3)	1 (16.7)	0 (0.0)	3 (16.7)	Unrelated	2 (33.3)	1 (16.7)	0 (0.0)	3 (16.7)
C-reactive protein increased	Unrelated	0 (0.0)	1 (16.7)	1 (16.7)	2 (11.1)	Unrelated	0 (0.0)	1 (16.7)	1 (16.7)	2 (11.1)
	Unlikely	1 (16.7)	0 (0.0)	0 (0.0)	1 (5.6)	Unlikely	1 (16.7)	0 (0.0)	0 (0.0)	1 (5.6)

†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.

Possibly: A reasonable causal relationship between the cell treatment/procedure and the AE. Information related to withdrawal of cell treatment/procedure was lacking or unclear.

Probably: 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.

Definitely: 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.

REFERENCES

1 Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, et al. Perioperative Management of Antithrombotic Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl):e326S-e350S.