

# Clinical Outcomes from a Multi-Center Study of Human Neural Stem Cell Transplantation in Chronic Cervical Spinal Cord Injury

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## Abstract

Human neural stem cell transplantation (HuCNS-SC<sup>®</sup>) is a promising central nervous system (CNS) tissue repair strategy in patients with stable neurological deficits from chronic spinal cord injury (SCI). These immature human neural cells have been demonstrated to survive when transplanted *in vivo*, extend neural processes, form synaptic contacts, and improve functional outcomes after experimental SCI. A phase II single blind, randomized proof-of-concept study of the safety and efficacy of HuCNS-SC transplantation into the cervical spinal cord was undertaken in patients with chronic C5–7 tetraplegia, 4–24 months post-injury. In Cohort I ( $n=6$ ) dose escalation from 15,000,000 to 40,000,000 cells was performed to determine the optimum dose. In Cohort II an additional six participants were transplanted at target dose (40,000,000) and compared with four untreated controls. Within the transplant group, there were nine American Spinal Injury Association Impairment Scale (AIS) B and three AIS A participants with a median age at transplant of 28 years with an average time to transplant post-injury of 1 year. Immunosuppression was continued for 6 months post-transplant, and immunosuppressive blood levels of tacrolimus were achieved and well tolerated. At 1 year post-transplantation, there was no evidence of additional spinal cord damage, new lesions, or syrinx formation on magnetic resonance (MR) imaging. In summary, the incremental dose escalation design established surgical safety, tolerability, and feasibility in Cohort I. Interim analysis of Cohorts I and II demonstrated a trend toward Upper Extremity Motor Score (UEMS) and Graded Redefined Assessment of Strength, Sensibility, and Prehension (GRASSP) motor gains in the treated participants, but at a magnitude below the required clinical efficacy threshold set by the sponsor to support further development resulting in early study termination.

**Keywords:** human; SCI; stem cells; tetraplegia; transplantation

## Introduction

PEOPLE EXPERIENCING the chronic, deleterious neurological and systemic effects of spinal cord injury (SCI) have few therapeutic options. Although neuroprotective strategies such as hypothermia,<sup>1–3</sup> riluzole,<sup>4</sup> and minocycline<sup>5</sup> among others are undergoing active investigation, they will not impact the chronic SCI population. Cell replacement strategies are critical in replacing the lost neural circuitry and/or myelination that can ensue after the gliosis, degeneration, and tissue atrophy with cystic cavitation that form the pathological hallmarks of chronic SCI.

Human embryonic stem cells are pluripotent and have been shown to be capable of reliably differentiating into neurons, oligodendrocytes, and astrocytes.<sup>6–11</sup> Another potential source of human central nervous system (CNS)-derived neural stem cell (NSCs) (e.g., HuCNS-SC<sup>®</sup>, Stemcells, Inc, Newark, CA) is fetal CNS tissue, which is relatively abundant in NSCs. NSCs can be multipotent or lineage-restricted to CNS cellular populations, and have been demonstrated in mouse SCI transplant models to facilitate recovery, both functionally and anatomically.<sup>12–15</sup> Cellular replacement therapies are one of the few treatments for SCI with the potential to rebuild the cellular architecture of the damaged spinal cord.

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HuCNS-SC safety has been demonstrated in several completed clinical trials including the experimental treatment of neuronal ceroid lipofuscinoses, a fatal lysosomal storage disorder,<sup>16</sup> Pelizaeus–Merzbacher disease,<sup>17</sup> an X-linked dysmyelination disorder that is predominantly a disorder of myelination, and dry age-related macular degeneration,<sup>18,19</sup> as well as chronic thoracic motor complete SCI (A. Curt, unpublished data, 2018). Human-derived NSCs also have demonstrated clinical safety in recent clinical trials for the treatment of amyotrophic lateral sclerosis (ALS), by providing motoneuron replacement.<sup>20</sup>

The techniques for the safe injection of intramedullary human Schwann cells,<sup>21</sup> HuCNS-SC,<sup>22</sup> and human spinal cord derived NSC<sup>23–26</sup> have been tested in animal models, including large porcine recipients, to further elucidate human upscaling cell dosage and volume. Although a group of investigators have raised the question of the minimum requisite safety and efficacy data for moving cell therapies into human trials in SCI, there are numerous end-point assessments that are unique to human injuries. Physiological motor assessments including assessments of dexterity can be difficult to obtain from experimental models even in non-human primates, in part because of the large contribution of the corticospinal tract size and direct corticomotoneuronal connections for voluntary movements in humans.<sup>27</sup> In addition, acquired or human pain syndromes, as well as the location, type, and intensity of pain cannot be reliably investigated in experimental animals. In the last few years, human cell transplantation trials have been published in subacute thoracic SCI,<sup>28</sup> chronic cervical SCI,<sup>22</sup> and ALS.<sup>20</sup> In the current phase II multi-center study, the authors report a minimum of 9 months of follow-up data for chronic cervical SCI treated with perilesional intramedullary transplantation with HuCNS-SC.

## Methods

### Experimental design

The investigational product, HuCNS-SC, was authorized as an investigational new drug (IND-15712) by the United States Food and Drug Administration (FDA). The trial was registered on ClinicalTrials.gov (NCT 02163876). The Quorum Institutional Review Board (IRB) served as the central IRB and evaluated and approved the cervical clinical trial for eligible participating centers; all other centers relied on their respective site IRBs for approval. Participant consent was obtained prior to any evaluations.

The original trial was designed to enroll 52 participants as a sequential investigation involving transplantation of allogeneic HuCNS-SC cells into three cohorts with chronic SCI. Cohort I was designed as an open-label dose escalation study and consisted of six subjects with International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) motor complete C5–C7 SCI (American Spinal Injury Association Impairment Scale [AIS] A or B). In this cohort, SCI participants received either 15,000,000, 30,000,000, or 40,000,000 cells, with two participants in each dose assignment. Cohort II consisted of participants with C5–7 motor complete (AIS A or B) SCI, and was used as a controlled, single-blind, randomized, parallel-arm comparison. Cohort III consisted of six participants with C5–C7 motor incomplete (AIS C) SCI ( $n=6$ ) and was designed as a dose escalation study.

### Inclusion and exclusion criteria

In the phase II open-label, single dose safety and preliminary efficacy study of HuCNS-SC cell transplantation, participants were 4–24 months post-injury,<sup>29</sup> with C5–C7 ISNCSCI motor levels, male and female, 18–60 years of age, with a single traumatic and non-penetrating SCI, based on magnetic resonance imaging (MRI),

with AIS Grade A or B. All participants were also required to be in generally good medical condition other than their injury, to have no contraindications for systemic immunosuppression, MRIs, or safe surgical exposure of the lesion area. The detailed inclusion and exclusion criteria are listed in the supplementary text (see online supplementary material at <http://www.liebertpub.com>).

### Enrollment and data reduction

A total of 64 individuals were enrolled in the trial (across Cohorts I and II), of whom 33 failed screening when the sponsor elected to conduct an unplanned early interim analysis (IA). Of the 31 who passed screening, 6 were included in Cohort I and 25 were included in Cohort II. For Cohort I, the open label, dose escalation cohort, all six participants were transplanted. We had 12 month follow-up data (adverse events [AE], tacrolimus, Upper Extremity Motor Score [UEMS], Graded Redefined Assessment of Strength, Sensibility, and Prehension [GRASSP], MRI) on all six participants; therefore, none were excluded from analyses. Of the 25 participants in Cohort II, 13 were randomized to treatment and 12 were randomized to control. The original pre-planned IA was powered to evaluate efficacy based on a minimum of 6 months of efficacy data in ~25 Cohort II subjects. For this unplanned IA, a new statistical analysis plan and rules for determining futility were formalized after careful consideration of subject matter expert input. The IA consisted of a review of the available interim data by an independent data monitoring committee, and resulted in an abrupt stop in recruitment and early study termination without continued monitoring of all participants entered into the protocol. For the 13 randomized to treatment, 11 were transplanted and the trial was halted before the last 2 could be transplanted. Of the 11 who were transplanted, we only have 3, 6, and 9 month post-transplant data (AE, Tacrolimus, UEMS, GRASSP, MRI) were available in 6 subjects, the results of which are the basis of this report. For the five who were excluded from data analyses, four had no accessible post-transplant follow-up data and one only had Day 28 UEMS data available. For the 12 randomized to control, only 4 had 3, 6, and 9 month follow-up data (AE, UEMS, GRASSP, MRI) and were included in data analyses. The other eight were excluded from data analyses because four of them were followed for 4 months and four were followed for <3 months when the trial was halted.

Participant demographics, including study site, gender, age, time post-injury, neurological level of injury, AIS grade, race and ethnicity, and cell dose are described in Table 1 for all transplanted and control participants included in this data analysis. Cohort I included two subjects for each of three escalation dosages for a total of six subjects. The article was written in accordance with Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.

Safety assessments included collection of AE reports coded using the Medical Dictionary for Regulatory Activities Terminology (MedDRA V11.0 or higher) dictionary. Any AE that resulted in death, was life-threatening, required in-patient hospitalization (or prolongation of existing hospitalization), or resulted in persistent or significant disability/incapacity, was considered a serious adverse event (SAE). The number and percentage of subjects with S/AEs were summarized for each treatment by maximum intensity and relationship to study treatment.

### Cell processing

HuCNS-SC cells were prepared and released by StemCells Inc. according to product manufacturing specifications and regulatory standards established with the FDA. The cells were shipped overnight in a 1 mL vial on ice via a commercial carrier. A proprietary temperature monitoring device allowed the recipient to confirm successful 4°C temperature control during shipping, which permitted

TABLE 1. DEMOGRAPHIC CHARACTERISTICS

Subject ID	Gender	Age	Time post-injury (years)	Neurological level of injury	AIS grade	Race/Ethnicity	Dose
<i>Cohort 1 – Open label, transplant, dose escalation</i>							
17-1002	M	24	1.4	C6	B	White/Non-Hispanic	15 × 10 <sup>6</sup>
13-1001	M	23	1.5	C6	B	White/Non-Hispanic	15 × 10 <sup>6</sup>
13-1002	M	27	1.8	C4	B	White/Non-Hispanic	30 × 10 <sup>6</sup>
17-1003	M	30	0.8	C6	A	White/Non-Hispanic	30 × 10 <sup>6</sup>
19-1001	M	23	1.6	C6	B	White/Non-Hispanic	40 × 10 <sup>6</sup>
18-1002	M	29	0.8	C6	A	White/Non-Hispanic	40 × 10 <sup>6</sup>
<i>Cohort 2 – Randomized, single-blind, transplant</i>							
15-1001	M	22	1.5	C6	B	White/Non-Hispanic	40 × 10 <sup>6</sup>
17-1005	M	48	0.4	C5	B	White/Non-Hispanic	40 × 10 <sup>6</sup>
18-1001	F	28	0.5	C4	A	White/Non-Hispanic	40 × 10 <sup>6</sup>
19-1003	M	24	0.7	C6	B	White/Non-Hispanic	40 × 10 <sup>6</sup>
19-1004	M	29	0.7	C4	B	White/Non-Hispanic	40 × 10 <sup>6</sup>
17-1008	M	33	0.8	C5	B	White/Non-Hispanic	40 × 10 <sup>6</sup>
<i>Cohort 2 – Randomized, single-blind, control</i>							
13-1004	M	27	1.0	C6	B	White/Non-Hispanic	NA
13-1005	F	29	1.9	C6	B	White/Non-Hispanic	NA
23-1001	M	24	0.8	C6	B	White/Non-Hispanic	NA
17-1007	M	49	1.1	C6	B	White/Hispanic	NA

AIS, American Spinal Injury Association (ASIA) Impairment Scale.

the surgical procedure to ensue. Lot release criteria testing was repeated at individual academic centers.

### Surgical technique

After induction of general anesthesia and intubation, the participants were placed in the prone position on the operating room table. Somatosensory and motor evoked potentials (SSEPS/MEPS) were used for spinal cord and nerve root monitoring.<sup>22</sup> Scar tissue and the paraspinal muscles were dissected to expose the underlying dura overlying the intended transplant sites. Intraoperative ultrasound imaging (Hitachi HI Vision Ascendus, Hitachi Medical Systems Europe Holding AG, Switzerland/12 MHz linear array transducer on an IU22 scanner [Hitachi Aloka Medical America, Inc., Wallingford, CT]) was used to visualize intramedullary architecture, especially cystic cavities, and was essential for defining the intraoperative rostral and caudal transplantation sites predicted from the preoperative MRI. The extent of dural opening was determined according to the ultrasound findings.

The surgical approach involved perilesional intramedullary injections of stem cells that were not specifically targeted to a designated anatomical motor tract. This was based on data from the nonobese diabetic–severe combined immunodeficiency (NOD-SCID) mouse spinal cord contusion model<sup>14</sup> in which extensive survival and migration of HuCNS-SC were observed following non-specific targeted intramedullary injections. The trajectory of the needle relative to the dorsal root entry zone (DREZ) was selected to avoid eloquent intramedullary structures, and the depth of the injection was determined by the preoperative axial MRI (3–5 mm below the dorsal surface). For details of surgical injection technique, see the study by Levi and coworkers.<sup>22</sup> In brief, the protocol mandated a rate of cell infusion of 20  $\mu$ L/min with a maximum time of injection of 3:30 min (70  $\mu$ L per injection site) followed by an additional 1 min dwell time to avoid reflux of cells along the needle tract before the needle was withdrawn. Stabilizing a hand-held syringe and

needle was critical for the time required for each injection (2:45–4:30 min), and using a two-hand technique with stabilization of the surgeons' hands on the wound side walls and retractors facilitated the process.

### Immunosuppression paradigm

Immunosuppressive agents were administered to participants undergoing stem cell transplantation to optimize HuCNS-SC cell engraftment. Tacrolimus was administered orally starting 3 days prior to surgery and for 6 months following transplantation. The dosage was calculated based on weight, and ranged from 0.1 to 0.15 mg/kg taken every 12 h. The dose was adjusted based on serum levels. Tacrolimus trough blood levels were monitored frequently and at the discretion of the site's immunosuppression specialist to obtain target blood levels of 5–10  $\mu$ g/L for first 28 days and 2–5  $\mu$ g/L for the following 5 months. Trimethoprim/sulfamethoxazole (6 months) and mycophenolate mofetil (MMF) (1 month) were administered in transplanted subjects to reduce the risk of stem cell transplant rejection. Dexamethasone and pantoprazole were also administered on the day prior to and for 7 days following transplantation.

### End-point assessments

Participants were monitored during scheduled visits to the investigation site for a maximum of 1 year after transplantation. Clinical assessments of the primary efficacy measure (ISNCSCI UEMS) and select secondary measures (ISNCSCI, GRASSP) were conducted by trained examiners blinded to each participant's treatment assignment for Cohort II. Secondary measures reported here also included tacrolimus blood levels, GRASSP, the Modified Ashworth Scale (MAS) to assess spasticity, a short pain assessment and allodynia questionnaire, AEs and SAEs, and MR lesion length on sagittal T2 weighted images.

### Statistical analysis

The primary efficacy interim analysis to determine study continuation was pre-determined and performed at StemCells Inc. Although this specific calculation is unavailable, it was the change from baseline in the ISNCSCI UEMS at Month 6 for Cohort II. With the current data, a two way mixed-model ANOVA was performed to assess significant differences between control ( $n=4$ ) and treatment groups ( $n=12$ ) with respect to UEMS, all three components of the GRASSP, and the MAS Upper Extremity (UE) and Lower Extremity (LE).

### Results

Subjects were enrolled in Cohorts I and II over a period of 19 months before the study was prematurely terminated. Demographic data for all participants and sites reported here are shown in Table 1. Nine of the transplanted individuals were AIS B and 3 were AIS A, with a median age at transplant of 28 years (range: 22–48 years) and an average time to transplant post-injury of 1 year (range: 0.4–1.8 years). The median time from injury to transplant was 0.77 years in the stem cell treated and 1.2 years to inclusion in the control groups respectively (Cohort II). A Consolidated Standards of Reporting Trials (CONSORT) diagram is included in Figure S1 for the University of Miami site only, as complete screening data were unavailable for all other sites (see online supplementary material at <http://www.liebertpub.com>).<sup>30</sup>

### Tacrolimus data

Data sets for Cohort I ( $n=6$ ) and Cohort II ( $n=6$  transplanted participants) for the first 6 months post-transplant are complete (Fig. 1). This demonstrates that there was mild variation in tacrolimus blood levels for the first 30 days while subjects were taking the higher dose of tacrolimus, which became minimal at the lower target dose. Similar blood levels were observed between Cohorts I

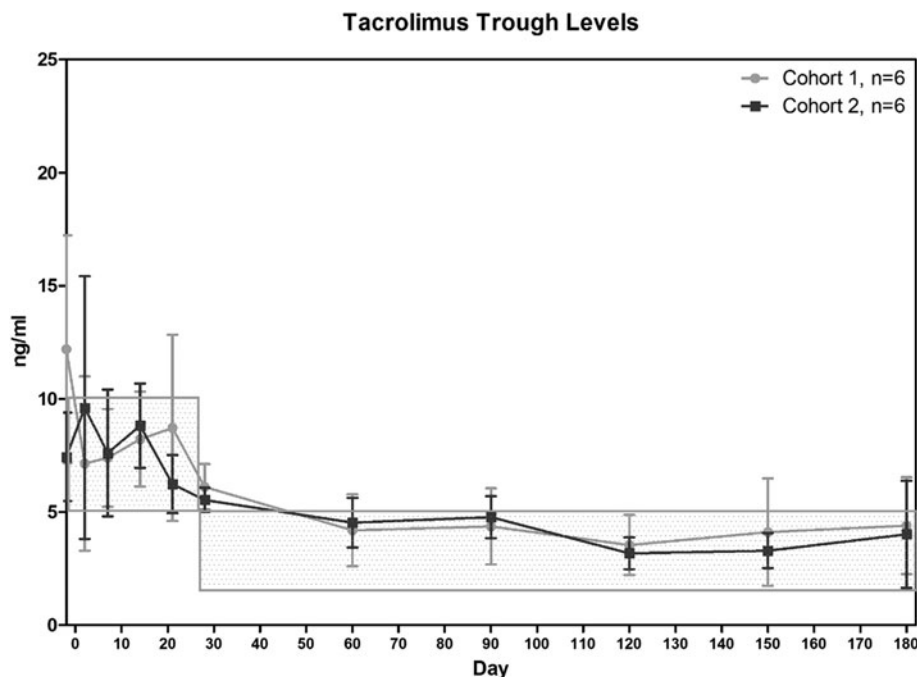
and II out to 6 months, and fell closely within target range. In the first 30 days, blood levels of tacrolimus were performed at the discretion of the immunosuppression physician, typically a transplant surgeon, at the local institution familiar with administration of this commonly used drug. Most importantly, the immunosuppression regimen was in general well tolerated, and no participants terminated immunosuppression early.

### UEMS

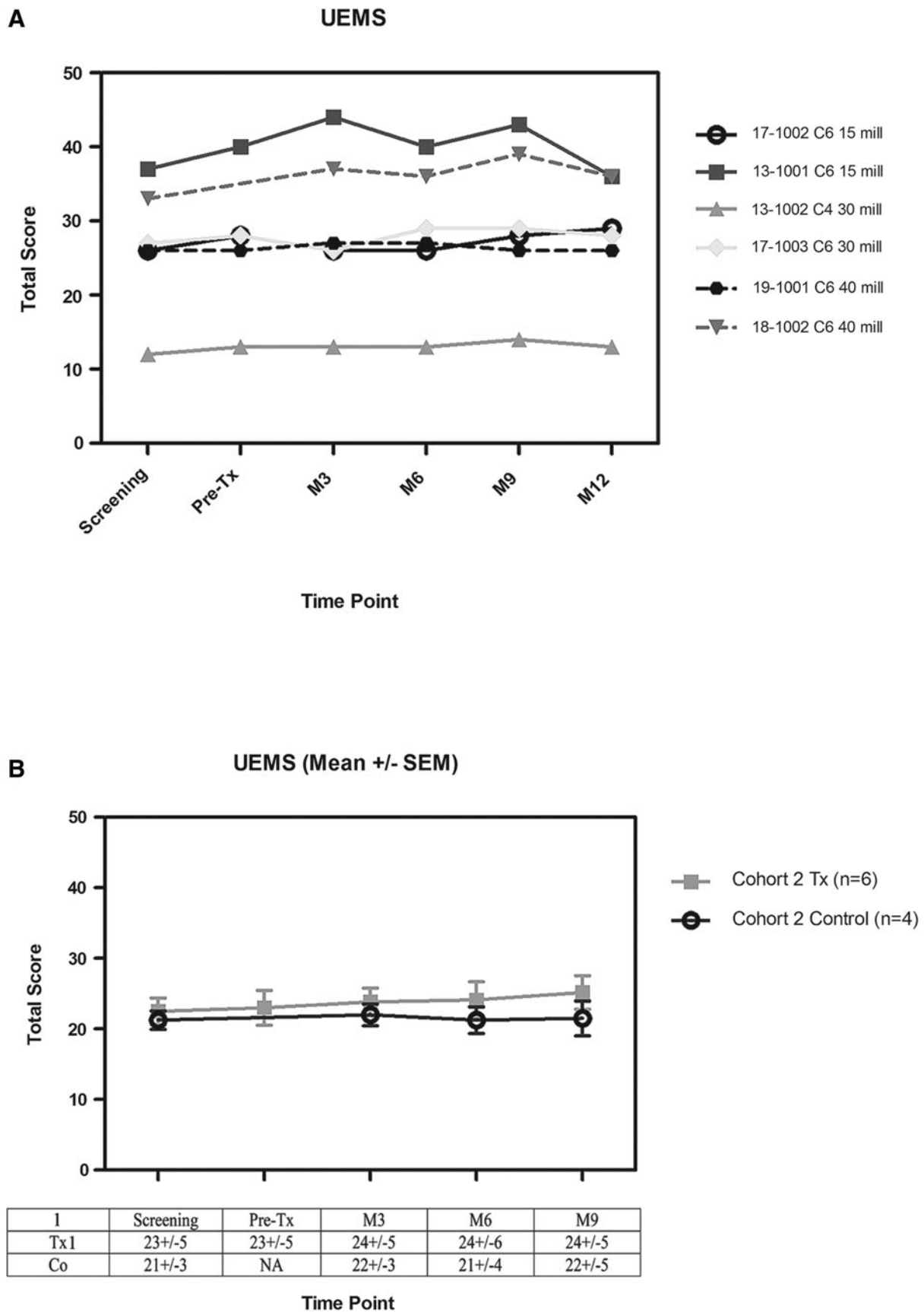
UEMS in both Cohort I (0–12 months) and in Cohort II (0–9 months) are presented (Fig. 2 A, B). One of the main findings is that over the period of observation in Cohort I (Fig. 2A) there was no decrement in UEMS status after intramedullary injection of stem cells. The crucial decision to move the 40,000,000 cell dosage to all treated participants in Cohort II was based on tolerance to the injection protocol. Of equal importance, higher stem cell dosage (40,000,000) of HuCNS-SC cells did not result in greater improvement in UEMS outcomes at 12 months than did the lower doses (15,000,000 and 30,000,000). In Cohort II (Fig. 2B), comparing treatment ( $n=6$ ) to control ( $n=4$ ) groups, the NSC-treated cohort UEMS increased over time and “pulled away” in terms of the lines separating from control. The mean difference between groups at screening was 1.25 points (Treatment Group [Tx] = 22.50, Control Group [Co] = 21.25). The mean difference between groups at 9 months was 2.83 points (Tx = 24.33, Co = 21.50). A two way ANOVA mixed-model (between [treatment] and within [time] groups) indicated no significant interaction between Tx and Co ( $p=0.2655$ ).

### GRASSP

The GRASSP is a clinical impairment measure specific to the upper limb for use after tetraplegia. It includes sensorimotor function



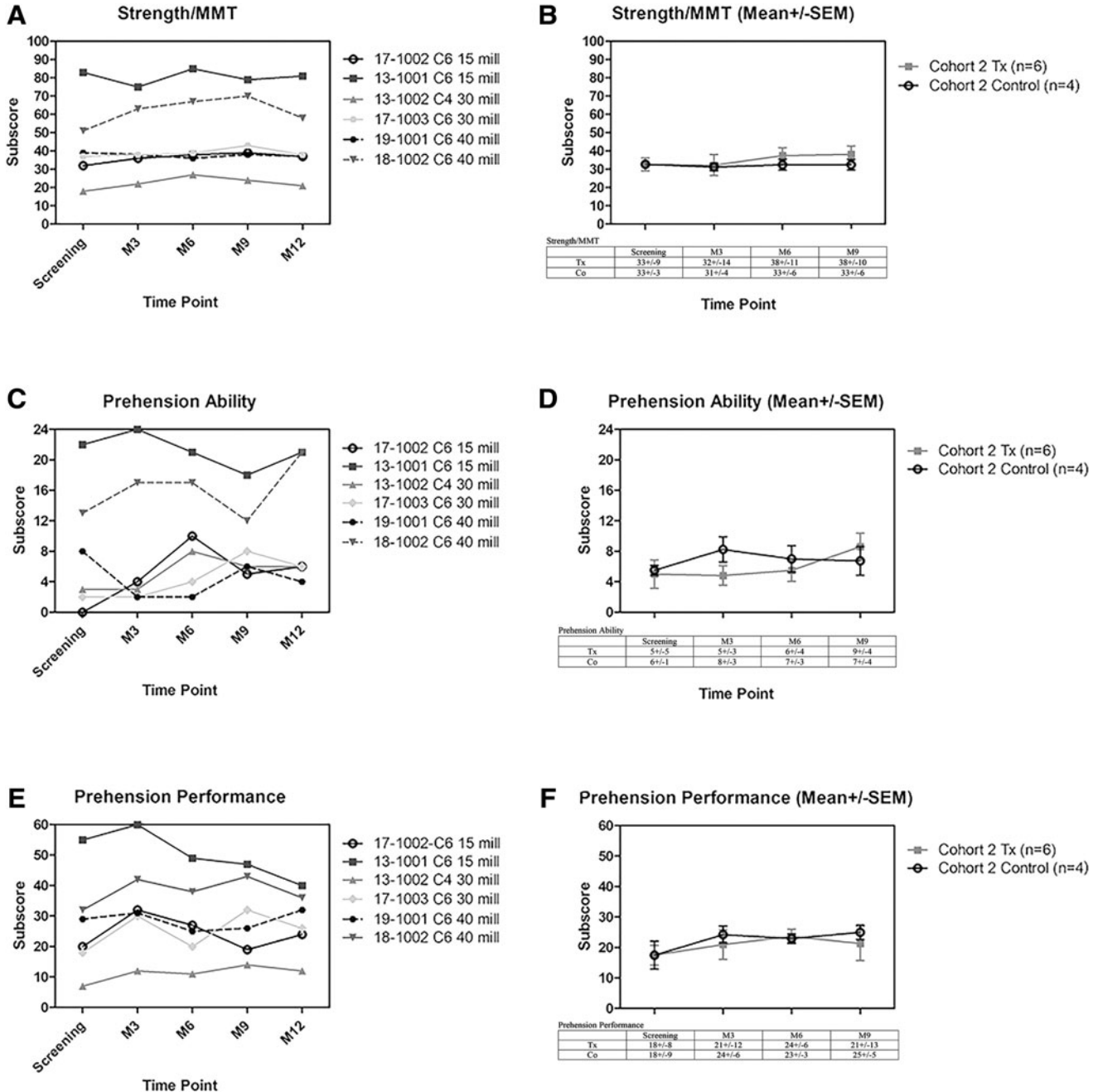
**FIG. 1.** Tacrolimus data from six transplanted patients in Cohort I (gray line) and six transplanted patients in Cohort II (black line) over a 6 month period. This demonstrates that there was mild variation in tacrolimus blood levels for the first 30 days while subjects were taking higher doses of tacrolimus, which became minimal at the lower target doses. Similar tacrolimus blood levels were observed between Cohorts I and II out to 6 months, and fell closely within target range.



**FIG. 2.** (A and B). Upper Extremity Motor Scores (UEMS) in both Cohort I from screening to month 12 and in Cohort II from screening to month 9. Results demonstrate no decrement in UEMS status after intramedullary injection of stem cells independent of cell dosage (Cohort I). In Cohort II (B), comparing treatment ( $n=6$ ) with control groups ( $n=4$ ), the stem cell treated cohort UEMS increased over time. The mean difference between groups at screening was 1.25 points and at 9 months it was 2.83 points.

in three domains for arm and particularly hand function with scores for strength, sensibility, and prehension ability and performance. GRASSP was performed at screening, and at 3, 6, 9, and 12 month intervals for Cohort I and in a blinded fashion at screening, and 3, 6, and 9 month intervals in Cohort II. GRASSP strength/manual muscle testing (MMT) and prehension ability and

performance are reported here for all participants (Fig. 3). Cohort I GRASSP data demonstrate safety of the intramedullary cellular injection at the earliest time point tested (3 months). GRASSP testing in Cohort I was performed both during the 6 months with immunosuppression and the 6 months without. In some participants – for example, 17-1002 – there were remarkable increases in GRASSP



**FIG. 3.** (A-F) Graded Redefined Assessment of Strength, Sensibility, and Prehension (GRASSP) strength, prehension ability, and performance are presented for both Cohort I (A, C, and E) and Cohort II (B, D, and F). GRASSP was performed at screening, and at 3, 6, 9, and 12 month intervals for Cohort I and in a blinded fashion at screening, and at 3, 6, and 9 month intervals in Cohort II. In Cohort I, GRASSP data demonstrate safety of the intramedullary cellular injection at the earliest time point tested (3 months). GRASSP testing in Cohort I was performed during 6 months with immunosuppression and during 6 months without. In some participants – for example, 17-1002 – there were remarkable increases in GRASSP scores at 6 months, but these results were not sustained at 12 months. In Cohort II, the GRASSP strength and prehension ability improved by 4.17 and 1.08 points while the prehension performance declined by 3.5 points between treatment and control over the first 9 months. No significant differences were seen between groups or over time using a two way ANOVA mixed model assessment.

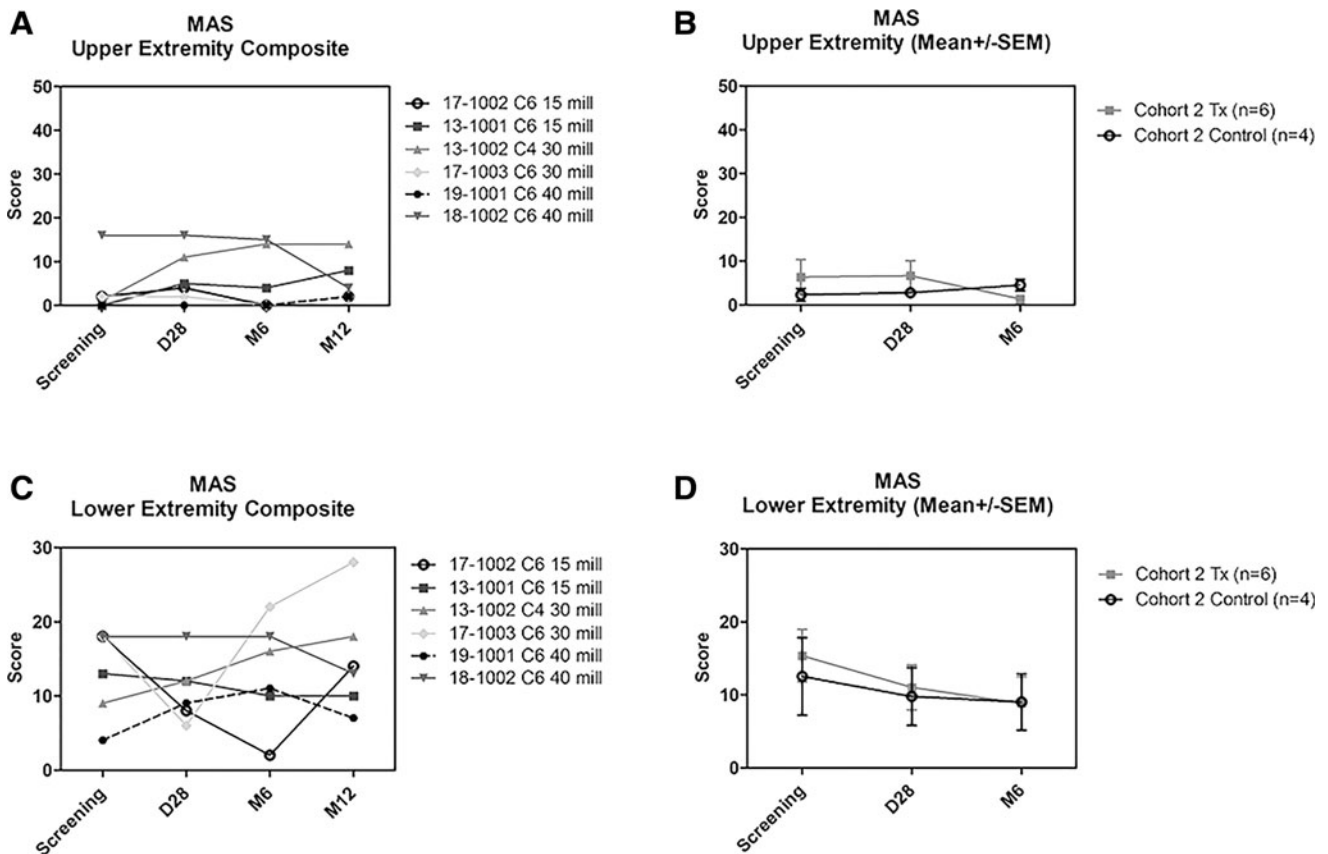
scores at 6 months, but these results were not sustained at 12 months. In Cohort II, the GRASSP strength and prehension ability improved by 4.17 and 1.08 points, while the prehension performance declined by 3.5 points between treatment and control groups over the first 9 months. No significant differences were seen between groups or over time using a two way ANOVA mixed- model assessment.

**Spasticity**

We evaluated the spasticity scores both in Cohort I and Cohort II and included both the upper and lower extremity assessments (Fig. 4). In Cohorts I and II, there was an overall stability of their spasticity in the upper extremities (Fig. 4A). In Cohort II, the treated group spasticity appeared to decline to a greater extent over the 6 month period of observation (Fig. 4 B and D). A two way ANOVA mixed-model (between [treatment] and within [time] groups) indicated no significant interaction between treatment and control. We also looked at the lower extremity spasticity in Cohort I (Fig. 4C), and particularly in the 30,000,000 cohort, there appeared to be an overall increase, whereas in Cohort II (Fig. 4D), the group analysis showed an overall reduction in spasticity compared with screening when evaluated at 6 months. We present clinical scores of spasticity, whereas patient-reported assessments of the impact of spasticity were not included in the study.

**Pain and allodynia assessments**

Of the six participants in Cohort I, two reported no pain at screening, temporary musculoskeletal neck pain at Day 28 post-transplant, and no pain at Month 12. Two other participants reported musculoskeletal pain around the neck region at screening, which persisted through Day 28 and Month 12 post-transplant. The intensity increased by 5 and 2 points, respectively, at Month 12. Another participant had a nociceptive pain in the pelvis/anus/calf region of unknown classification at screening, which resolved by Day 28 and Month 12, and transient musculoskeletal shoulder pain at Day 28. Only one participant reported neuropathic pain, which was first reported at Month 12 and was below level in the lower back. For Cohort II, pain data are only available for screening and Day 28, as the study was prematurely terminated before any participants reached Month 12. Three of the six transplanted participants reported no pain at screening or Day 28. Two reported no pain at screening and musculoskeletal pain in the head/neck/shoulder region at Day 28. One transplanted participant reported musculoskeletal shoulder pain at screening, which was not reported at Day 28; however, at Day 28, there was musculoskeletal neck pain and neuropathic below-level pain in both thighs, calves, and feet. None of the four control participants in Cohort II reported pain at screening or on Day 28. Additional details for all participants are available in the Table S1 (see online supplementary material at <http://www.liebertpub.com>).



**FIG. 4.** (A–D) In Cohorts I and II, there was an overall stability of their spasticity in the upper extremities (A). In Cohort II, the treated group spasticity appeared to decline over the 6 month period of observation (B and D). The lower extremity spasticity in Cohort I (C), particularly in the 30,000,000 cohort, appears to demonstrate an overall increase whereas in Cohort II (D), the group analysis showed an overall reduction in spasticity.

## AEs

AEs and SAEs were reported (Table 2). As with many trials involving SCI participants, there can be many AE and SAEs recorded for any time during the period of study. There was a total of nine SAEs in the 12 transplanted participants, an average of 0.75 per participant although three SAEs occurred in one participant. There was a total of two SAEs in the four control participants: an average of 0.5 per participant. Although no SAEs could be directly ascribed to injection of HuCNS-SC into the spinal cord around the lesion epicenter, there were two SAEs related to the surgical incision, including a staph epidermidis wound infection requiring incision and drainage and IV antibiotics, as well as a non-surgical incisional hematoma. This represents 2 of the 12 transplanted participants and underscores the significance of the invasive nature of the procedure. Supporting the safety of this protocol was that there was only one infection-related surgical SAE in the stem cell treated group during the period of immunosuppression.

## MRI and lesion length

MRI with and without gadolinium of the cervical spinal cord and brain was performed at baseline pre-transplantation and cervical MR was performed at 1–3 days, 6 months, and 12 months post-transplantation. Inclusion criteria included a maximum lesion length of 5 cm on T2 weighted MRI. The lesions were heterogeneous in appearance. Certain screened participants were excluded simply for large lesion size (Fig. S1; see online supplementary material at <http://www.liebertpub.com>). Lesion length at screening varied from 0.69 to 4.43 cm, with an average lesion length in transplanted participants of 2.43 cm. At the last follow-up of 6 or 12 months, lesion length varied from 0.65 to 4.39 cm, with an average lesion length of 2.39 cm (Table 3). There were no instances of spinal cord hemorrhage on the immediate postoperative MRI, which potentially can be attributed to the effectiveness of intraoperative ultrasonography (IOUSG) in avoidance of spinal cord vasculature.<sup>3</sup> In Cohort I, 1 year MR follow-up data demonstrated the presence of a laminectomy and no significant spinal cord tethering, myelomalacia, cyst formation, kyphosis,

TABLE 2. ADVERSE EVENTS (AEs) AND SERIOUS ADVERSE EVENTS (SAEs)

Cohort	No. participants	Total AEs	No. that were SAEs	No. related	No. possibly related
I	n=6	48	2	10	3
II – Treatment (Tx)	n=6	55	7	10	10
II – Control (Co)	n=4	12	2	0	0

Category	Cohort I	Cohort II Tx	Cohort II Co
Cardiac disorders	0	0	1
Gastrointestinal disorders	8	6	0
General disorders and administration site conditions	0	2	0
Infections and infestations	12	16	9
Injury, poisoning, and procedural complications	7	7	2
Investigations	1	4	0
Metabolism and nutrition disorders	1	0	0
Musculoskeletal and connective tissue disorders	7	3	0
Nervous system disorders	7	9	0
Psychiatric disorders	1	0	0
Renal and urinary disorders	0	3	0
Reproductive system and breast disorders	0	1	0
Respiratory, thoracic, and mediastinal disorders	2	1	0
Skin and subcutaneous tissue disorders	2	1	0
Vascular disorders	0	2	0

Cohort I: SAEs (n=2)	Participant
Hospitalization: Wound infection – staphylococcal	17-1003
Hospitalization: Fecaloma	19-1001

Cohort II Control: SAEs (n=2)	Participant
Hospitalization: Urinary tract infection	13-1004
Hospitalization: Urinary tract infection	13-1004

Cohort II Transplant: SAEs (n=7)	No. participants
Hospitalization: Sepsis	17-1005
Hospitalization: Posterior reversible encephalopathy syndrome	18-1001
Important medical event: Seizure	18-1001
Important medical event: Wound hematoma	19-1003
Hospitalization: Autonomic dysreflexia	19-1003
Hospitalization: Seizure	19-1003
Hospitalization: Autonomic dysreflexia	19-1004



TABLE 3. MAGNETIC RESONANCE IMAGING (MRI) LESION LENGTH

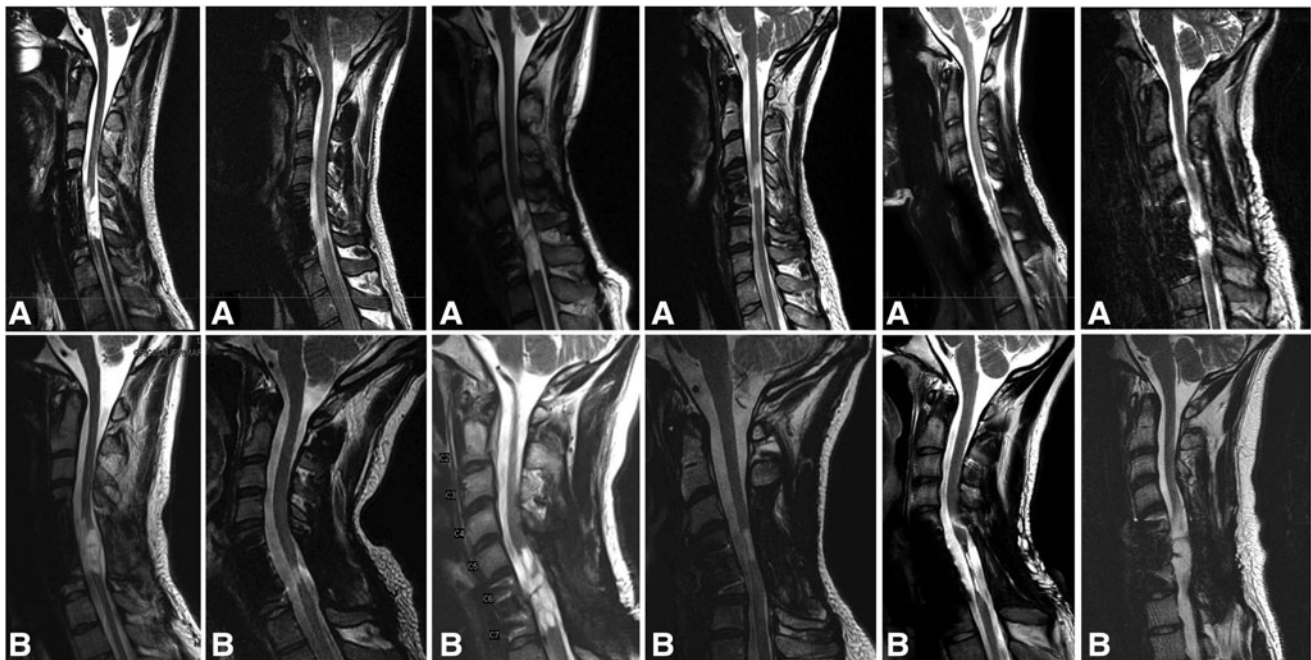
		13-1001	13-1002	17-1002	17-1003	18-1002	19-1001
<i>Cohort I</i>							
MRI-Length (cm)	Screen	1.399	1.727	3.16	4.43	3.292	3.667
	M6	1.5	1.732	3.49	4.36	3.292	3.58
	M12	1.447	1.599	3.27	4.39	3.292	3.63
		15-1001	17-1005	17-1008	18-1001	19-1003	19-1004
<i>Cohort II Transplant</i>							
MRI-Length (cm)	Screen	2.664	2.56	1.066	0.692	2.891	1.604
	M6	2.292	2.54	1.05	0.653	2.81	1.76
		23-1001	13-1004	13-1005	17-1007		
<i>Cohort II Control</i>							
MRI – Length (cm)	Screen	2.521	1.253	1.413	1.06		
	M6	2.52	1.533	1.439	1.11		

or instability (Fig. 5). One finding previously reported<sup>22</sup> included mild increased T2 signal change in half of transplanted participants at the intramedullary injection site rostral or caudal to the lesion epicenter without motor decrements or emerging neuropathic pain. All T2 new post-transplantation signal changes resolved by 6–12 months post-transplant.

**Discussion**

HuCNS-SCs transplantation have been repeatedly demonstrated in animal models of contusive SCI when transplanted to engraft, survive, migrate, and differentiate into neurons, astrocytes, and

oligodendrocytes.<sup>31–35</sup> As there was safety in two phase I studies<sup>17,18</sup> in the brain and retina completed using HuCNS-SC, interest and support has been mounting for transplantation of these cells in the setting of chronic thoracic and cervical SCI. NSC transplantation in the chronic time period, as compared with the acute time period, may provide a more favorable, less-inflammatory environment for cell engraftment. Finally, in studying individuals with chronic and stable deficits, as opposed to studying those in the acute or subacute period after SCI, there is greater confidence that any neurological improvement seen after transplant is attributable to the transplant rather than to natural evolution, as some degree of natural recovery is expected in the latter which may confound results.



**FIG. 5.** Sagittal T2-weighted magnetic resonance images (MRI) of pre-transplant appearance (A - upper row) of the cervical spinal cord of patients in Cohort I with chronic motor complete injury. Left to right represent ascending doses from 15,000,000 to 30,000,000 and 40,000,000 with two in each group. (B) In the bottom row are the 12 month post-operative MRIs that demonstrate a stable lesion length without evidence of tethering or the cavitation of syrinx formation.

In this phase II multi-center trial in chronic cervical SCI, human neural stem cell transplantation was safe, feasible, and well tolerated. Trends toward improvement in motor function and spasticity were seen, but with limited follow-up because of premature termination of the study by the sponsor. These findings could not be confirmed in a larger series of subjects with 12 months of follow-up.

### *Safety of surgical technique*

Safety outcomes for any phase I or II trial are of paramount importance, particularly when a cell transplantation paradigm is employed. The results of safety focusing on the technique of hand-held cellular injections<sup>26</sup> have been previously reported and the overall number of AEs and SAEs and the relationship to the surgical technique in all transplanted participants reported have been reviewed here. The essence of the study results suggested that hand-held injections in a perilesional location of the spinal cord are safe even at doses as high as 40,000,000 cells (total intramedullary volume of 560  $\mu$ L) delivered via eight (four above and four below) separate injections into the dorsal columns. Although a number of SAEs were observed in relation to the surgical procedure, no neurological AEs were specifically attributable to the spinal cord injections.

### *Cell survival and immunosuppression*

Although the central nervous system is considered a “relatively” immune privileged site for transplantation, determining cell survival of a transplanted cell is also of great importance, especially when the cell originates from an allogeneic source. The results of phase I studies involving HuCNS-SCs transplantation into multiple cerebral sites (as well as intraventricular in neuronal ceroid lipofuscinoses [NCL]) in pediatric subjects with NCL and Pelizaeus–Merzbacher disease (PMD) after 9 and 12 months of immunosuppression have been published.<sup>17,18</sup> MRI signal change in diffusion tensor imaging demonstrated cell engraftment and evidence of donor-derived myelin in the transplanted host white matter in the PMD study.<sup>17,18</sup> Post-mortem examination of subjects in the NCL study also demonstrated the survival of donor cells well after the planned withdrawal of the immunosuppression.<sup>17</sup>

### *Neurological recovery after chronic SCI*

One of the most important aspects when conducting a clinical trial is deciding how much neurological improvement would warrant a claim of “success.” Certainly a person with a chronic deficit might accept a lower threshold of improvement than a scientist, clinician, regulatory agency, or corporate entity. In this trial, a pre-specified futility analysis, conducted by the company, concluded that the improvement compared with controls observed at the interim analysis was insufficient to reach statistical significance for the primary endpoint of change from baseline in UEMS, and the trial was therefore prematurely terminated. This futility analysis was inherently limited, given that it was based on an underpowered subset of the accruing data required for a statistically relevant determination of efficacy.

In medicine, criteria for a “meaningful clinically important difference” (MCID)<sup>36</sup> have been established for a number of neurosurgical procedures.<sup>37</sup> Medical insurance companies are incorporating these data into their formulas to determine payments. In that therapies for chronic SCI are at a development or research stage, it is unfortunate that there is no consensus on the definition of MCID in SCI.<sup>38</sup> As emerging treatments including invasive surgical procedures<sup>39–42</sup> evolve in the field of SCI, a consensus needs

to be developed regarding what are the minimum thresholds for significant and clinically meaningful improvements.

In that many of the *chronic and neurologically stable* SCI participants who entered into Cohorts I and II and received the cell transplant improved in UEMS and certain components of the GRASSP enrolling in the trial an average of 1 year after injury, one would interpret that this would be the result of injection of the HuCNS-SC. In our study, there were no improvements in UEMS and GRASSP strength/MMT in the control group over a period of 9 months. Similarly, in the Phase I/II chronic thoracic SCI/Hu-CNS-SC trial (NCT 01321333), more than half of the participants (7/12) experienced sensory improvements after neurological stability from their chronic injuries (Curt, manuscript in preparation). For approximately half of those (3/7), the sensory improvements covered multiple segments distal to the level of the lesion (Curt, manuscript in preparation). A decline in sensory gains lost after withdrawal of the immunosuppressive agents is suggestive of biological activity resulting from the NSC transplants. There was no conversion of AIS grade after NSC transplantation, suggesting that in the setting of chronic cervical SCI, any beneficial effect was not mediated by long tract recovery. Segmental recovery can be detected by UEMS and GRASSP. GRASSP testing was designed as a clinical research tool to assess the degree of upper limb impairment in tetraplegia.<sup>43–45</sup> It captures integrated sensory/motor data and can distinguish levels of function, be responsive (sensitive) to change over time, assess the extent of spontaneous (natural) recovery, and importantly, be applied in clinical settings and in clinical trials/studies to evaluate the effect of novel interventions. The GRASSP scoring tool is 50% more sensitive than ISNCSCI for evaluating sensory and motor function of the upper limb, with a high interrater reliability (0.84–0.96).<sup>43,46,47</sup>

### *The future of cell-based therapies for SCI*

One of the major flaws of the current trial is its premature termination based on a pre-determined futility analysis. The result was enrollment of SCI participants into a trial with an invasive intervention without adequate follow-up and with potentially harmful consequences. At many sites, the academic host institution had to take on ethical and financial responsibility for patient care and data acquisition. Unfortunately, this is not the first time that SCI trials have been prematurely discontinued for primarily financial considerations (i.e., not based on safety concerns).<sup>48</sup> In each case, the absence of timely and complete collection of data has the potential to set the field of SCI cell transplantation research backwards and harm the physician–patient relationship. Even with what would be considered a negative trial with regard to the primary outcome measure (such as the current one), the investigators as scientists and clinicians learned a great deal, including but not limited to participant screening obstacles, lesion size differences despite similarities in neurological level, the safety of cell dosage/volume and spinal cord targets, methods of cell injection, and utility and limitations of primary and secondary end-points. This information, when disseminated through the appropriate portals, will allow future trials to be improved and prevented from repeating errors of past failures. In addition to excellent pre-clinical safety and efficacy data, we would also strongly advocate for clearer termination rules, including an orderly exit plan, as an absolute pre-requisite for regulatory approval, to optimize safe and effective clinical translation. When a well-justified decision to terminate a clinical research study is reached, it is imperative that the sponsor (corporate, governmental, or university) continues to ensure follow-up clinical

evaluations for all participants who have entered the trial. Requiring sponsors to guarantee sufficient funds up front to safeguard follow-up for each participant can ensure this. Although fledgling sponsors may find up-front funding guarantees difficult to achieve, an insurance policy to cover adequate follow-up in case of insolvency might be an option so as not to deter the pursuit of medical innovations undertaken by startup companies.

## Conclusion

This study revealed reliable safety and feasibility for HuCNS-SC transplantation into persons with chronic cervical SCI supported by repeated neurological, functional assessments, AE and SAE evaluations, and imaging over 12 months. Improvements in overall UEMS and GRASSP strength component at final follow-up were observed in those who received hand-held perilesional injections of HuCNS-SC. However, the full impact of HuCNS-SC could not be assessed, because of premature termination of the trial based on an underpowered *a priori* futility analysis.

## Acknowledgments

This work was supported by StemCells, Inc. and the respective Academic Institutions. Bright Oceans Corporation (BOCO) provided funds for post-termination data collection. We acknowledge all of the team members who contributed to the trial, including site members listed here. Most importantly, we are indebted to all of our participants and their families for deciding to participate in this trial and contribute to the advancement of our field. Site members in addition to primary authors included in trial:

1. University of Miami site: Marine Dididze, Katie Gilsenan, George Burke, Jasmine Martinez, Gabriel Sunn, Efrat Saraf-Lavi, Kevin Dalal, Jay Grossman, Diane Colabella, and George Jimshelishvili.
2. Icahn School of Medicine at Mount Sinai Site: Amish Doshi, Veronica Delaney, Irene Osborn, Patrick McCormick, Rebecca Kent, Miguel Escalon, Jessica Robinson-Papp, Arthur Jenkins, Hannah Kaplan, Roberto Rapalo, Alexandra Voight, Ashley Friend, Rozalyn Hesse, and Allan Kozlowski.
3. University of Michigan site: Michael Wheaton, Anthony Chiodo, Heidi Zayan, and Karen Frisch.
4. University of Pittsburgh site: Janice Alicandro, and Michael Munin
5. University of Maryland site: Charelene Aldrich and Kaitlyn Henry.
6. University of Wisconsin site: Laura Wollenweber, Charlotte Klis, Michelle Wesline, and Joanna Delap.

Primary investigators and sites that participated but were not included in trial because of inadequate length of follow-up: Dong Kim, MD, Department of Neurosurgery, University of Texas Health Science Center, TX; James S. Harrop, MD, Department of Neurosurgery, Thomas Jefferson University Hospital, Philadelphia, PA; Ann Parr MD, PhD, Department of Neurosurgery, University of Minnesota, Minneapolis MN; Aruna Ganju, MD, Department of Neurosurgery Northwestern University, Chicago, IL.

## Author Disclosure Statement

Dr. Allan D. Levi receives a teaching honorarium from the American Association of Neurological Surgeons (AANS) and grant support from the Department of Defense. Dr. Paul Park is a con-

sultant with Globus, Medtronic, Zimmer, and Nuvasive. He receives royalties from Globus and grant support from Pfizer. Dr. Kim D. Anderson is a consultant for Vertex Inc. Jane Hsieh is a former consultant with Stem Cells Inc. Dr. Thomas N. Bryce receives grant support from the Craig H. Neilsen Foundation and the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR). The other authors have nothing to disclose.

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