BrainStorm Releases Clinical Trial Results

Company Note

BrainStorm Cell Therapeutics (OTC QB: BCLI) released positive results from its Phase I/II trial of *NurOwn*™ cells for treatment of amyotrophic lateral sclerosis (ALS). The data were presented at the American Academy of Neurology conference on March 20th, 2013. In addition to meeting the primary endpoints of safety and tolerability, the trial results indicated initial signs of efficacy.

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BrainStorm Chosen for Emerging Science Session at AAN. This week, BrainStorm Cell presented Phase I/II data from a trial of its *NurOwn* cells for the treatment of ALS. The presentation at the American Academy of Neurology (AAN) annual meeting was selected for the Emerging Science Session, which highlights exciting new research that is specifically chosen for expedited presentation. Selection for an Emerging Science presentation is an important validation of the potential of *NurOwn* cells to treat ALS. The trial data presented point to a strong safety profile and initial efficacy signal for the *NurOwn* cell therapy. Further details about the trial and data presented are included below.

Mayo Clinic to join Phase II Trial of *NurOwn* Cells for ALS. On Monday, March 18, BrainStorm announced that the Mayo Clinic in Rochester, Minnesota intends to participate in the Company's Phase II trial of *NurOwn* cells for the treatment of ALS. Following the University of Massachusetts and the Massachusetts General Hospital, the Mayo Clinic is now the third clinical site that will participate in the trial. Recruitment for the trial is expected to begin in the second half of 2013.

Ticker	BCLI
Price	$0.24
Market Cap (M)	$36.2
EV (M)	$33.5
Shares Outstanding (M)	150.9
Fully Diluted Shares (M)	218
Avg. Daily Vol.	188.578
52-week Range:	$0.17-0.38
Cash (M, pro forma)	$4.0
Net Cash/Share	$0.03
Debt (M)	$1.3
Annualized Cash Burn (M)	$4
Years of Cash Left	1
Short Interest (M)	N/A
Short Interest (% of Float)	N/A

FY Dec		2011A	2012A	2013A
EPS:	Q1	($0.01)A	($0.01)A	N/A
	Q2	($0.01)A	($0.01)A	N/A
	Q3	($0.01)A	($0.01)A	N/A
	Q4	($0.01)A	N/A	N/A
	FY	($0.03)A	N/A	N/A

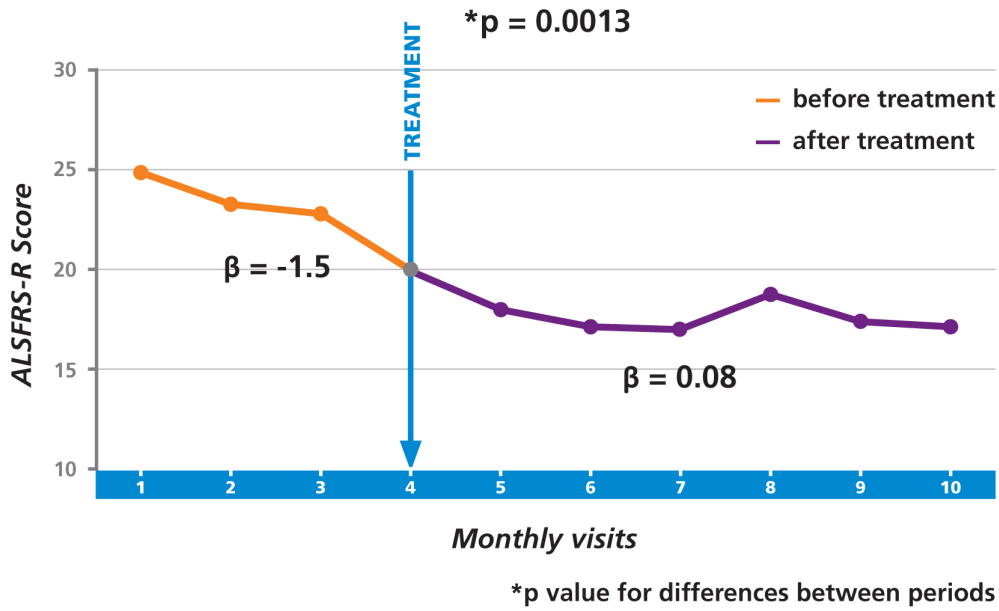
Background and Design of *NurOwn* Phase I/II Trial. BrainStorm has announced some of the final results from the Phase I/II trial of its *NurOwn* cells, which are autologous mesenchymal stem cells differentiated to express neurotrophic factors (MSC-NTF). The interventional, non-randomized study was designed to establish the safety and tolerability of the Company's *NurOwn* cells. 12 patients were followed in parallel groups of early and late stage ALS as determined by their respective Amyotrophic Lateral Sclerosis Rating Scale-Revised (ALSFRS-R) scores over three months pre-therapy. The early-stage ALS patients (n=6), those with ALSFRS-R scores >30, were then administered autologous MSC-NTF cells via intramuscular (IM) injections at 24 separate sites in the biceps and triceps. Progressive stage ALS (ALSFRS-R score from 15 to 30) patients (n=6) were administered a single intrathecal injection (IT) of autologous MSC-NTF cells directly into the spinal canal. Patients were then monitored for 6 months post treatment. Of note, only ALS patients with disease duration of less than two years and with at least 60% forced vital capacity (FVC, an indicator of respiratory function) were accepted to the study. Some key exclusion criteria included respiratory dependence, and EMG-confirmed slow nerve conduction velocities.

The primary safety evaluation and tolerability study endpoints were reached, with no serious treatment-related adverse events. Secondary outcome measures were a decreased progression rate of the disease as evidenced by ALSFRS-R score and FVC in the 6 late-stage, intrathecally-injected patients. Throughout the study, monthly measurements were made with respect to ALSFRS-R, FVC, body weight, BMI, physical and neurological examination, vitals, muscle bulk, muscle circumference and concomitant drug use. Bi-monthly measurements were made with respect to EMG, CBC, blood biochemistry, coagulation tests, immunology tests and urinalysis.

Results from Phase I/II Clinical Trial. The positive study results indicating a slower decline in ALSFRS-R and FVC scores of progressive stage patients after IT treatment were statistically significant. The remainder of data analysis and the study completion are estimated in May 2013. As presented in **Figure 1**, significant decreases in the rate of ALSFRS-R decline were seen ($p=0.0013$); this is evident when comparing beta coefficients for the pre-treatment and post-treatment periods.

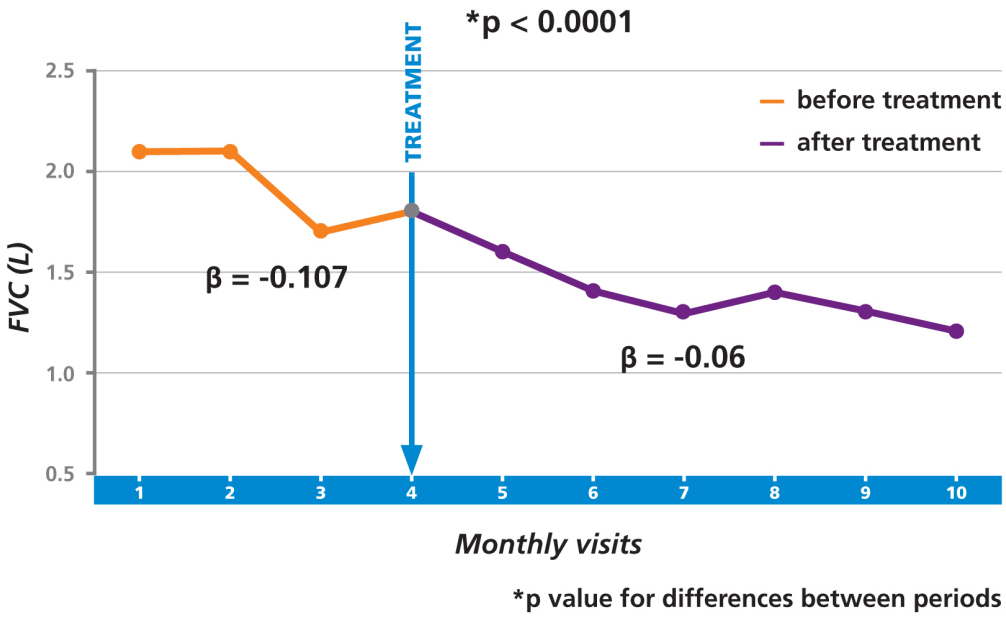
Additionally, a significant decrease in the rate of FVC decline ($p<0.0001$) was seen over the study period as seen in **Figure 2**, when comparing beta coefficients for the pre-treatment and post-treatment periods. ALSFRS-R is one of the primary rating instruments used to monitor ALS progression. The scale assigns a total of 48 points to various abilities, with a lower score indicating worse prognosis. Additionally, respiratory ability and thus FVC are important measures in cases of ALS. Terminal stages of ALS occur as motor neuron degeneration resulting in atrophy of respiratory muscles. Eventually, patients lose the ability to breathe autonomously and must use a mechanical ventilator. Both findings from **Figure 1** and **Figure 2** suggest a trend toward possible stabilization of the disease. Release of the final study details and completion of the company's current dose-escalating Phase IIa study are needed to confirm this trend.

Figure 1: Significant Decrease in Mean Rate of Change in ALSFRS-R Score Following Treatment with MSC-NTF Cells in IT-Transplanted Patients



Source: American Academy of Neurology Conference poster

Figure 2: Significant Decrease in Mean Rate of Change in Forced Vital Capacity (FVC) Following Treatment with MSC-NTF Cells in IT-Transplanted Patients



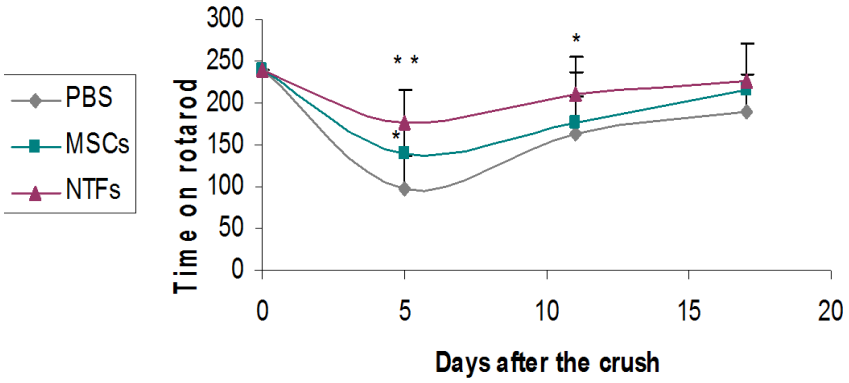
Source: American Academy of Neurology Conference poster

BrainStorm's Proprietary Production Process. For the clinical trial, BrainStorm sourced each patient's mesenchymal stem cells, expanded those cells using a proprietary growth medium, and induced the expanded cells to differentiate into MSC-NTF. NTF secretion was then used to confirm cell activity and potency prior to transplantation.

Strong Pre-Clinical Data Supports the Use of Mesenchymal Stem Cells to Treat ALS. Pre-clinical animal models have been successful. Neurotrophic factors have had therapeutic effects in motor nerve damage animal models. Mutations in the SOD1 gene are known to cause inherited ALS. A mouse model involving mice engineered to express human SOD1 provides data to support use of neurotrophic factors in cases of inherited ALS. Transgenic SOD1 mice were administered an adenovirus vector for Glial cell derived neurotrophic factor (GDNF) via intramuscular injection. Expression of GDNF in spinal cord motor neurons was later confirmed using chemoluminescence. The adenovirus GDNF vector treated mice lived 8 days longer then sham-treated and untreated mouse control groups.[1]

The cause for sporadic ALS is unknown; however the common pathology in all cases of ALS is motor nerve degeneration. Sciatic nerve crush was used to model neurodegenerative nerve injury, as it models lower limb paralysis and deficits that occur in diseases like ALS. Rats with sciatic nerve damage experienced significant inhibition of neuromuscular degeneration and also experienced quicker recovery when MSC-NTF cells were injected directly into the lesion as compared to placebo treated rats (PBS) and control treated (MSC) rats. These results are shown in **Figure 3**, where MSC-NTF treated rats show a quicker recovery as measured by their ability to run and balance themselves on a rotarod just five days after sciatic nerve crush.[2]

Figure 3: Intramuscular Injection of Rat NTF Cells Protects Against Mechanical Crush of Sciatic Nerve in Rats of Change Pre- and Post-Treatment



Source: Dadon-Nachum, M. et al., 2011.

[1] Acsadi, G. et al., 2002. Increased survival and function of SOD1 mice after Glial cell-derived neurotrophic factor gene therapy. *Human Gene Therapy*, 10(13), pp1047-1059.
[2] Dadon-Nachum, M. et al., 2011. Differentiated Mesenchymal Stem Cells for Sciatic Nerve Injury. *Stem Cell Reviews and Reports*, 7(3), pp664-671.

ALS Background. Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a degenerative disease of motor neurons with muscle atrophy secondary to denervation of the muscle. BrainStorm has focused on treatment of ALS using mesenchymal stem cells that have been differentiated to secrete neurotrophic growth factors (MSC-NTF). Neurotrophic growth factors promote survival of motor neurons. Pharmacological treatments for ALS are currently extremely limited, and stem cell treatments are seen as an alluring potential entrant into the market of ALS therapies.

Patients diagnosed with ALS are lacking treatment options. The national ALS registry reports the prevalence of ALS to be between six and eight cases per 100,000 people for an estimated 22,000 ALS cases in the United States. The only FDA approved drug used to slow ALS progression is Sanofi's *Rilutek* (riluzole). Riluzole treated patients on average experience a 10% increase in survival past 12 months when compared to untreated ALS patients this translates to an average increased survival of 3 months[3] or 6 months[4] depending on the study. Riluzole has also not been observed to have an impact on advanced cases of ALS[4] and is known to be associated with liver damage in some cases.

The use of growth factors to treat ALS is a rational approach. Evidence points to multiple causes of ALS; only 10% are familial with the remaining 90% being sporadic and attributed to a multiple of factors. The common theme with all instances of ALS is nonetheless a common clinical course and neuropathology of progressive degeneration of motor neurons leading to muscular atrophy, as such strengthening the neuromuscular junction and motor neuron cell bodies with growth factors is a rational approach.[5,6]

BrainStorm's use of autologous stem cells and delivery method addresses treatment concerns related to neurotrophic growth factors. Some of the concerns regarding ALS treatment with growth factors, namely method of drug delivery to the CNS along with associated pharmacokinetic considerations[4] and the inability of a single growth factor to necessarily address the several etiological mechanisms relevant to ALS[4] are addressed via BrainStorm's treatment methods.

The method of MSC-NTF administration brings about several considerations including the possibility of immune rejection, delivery time of treatment, and concentration of treatment to reach afflicted motor neurons. The use of autologous cells reduces risk of rejection. With IM administration of MSC-NTF close to the motor end plates, the neurotrophic factors secreted by the transplanted cells are expected to be taken up by the long axon terminals (nerve cell endings) in the muscle and transported back into the cell bodies in the spinal cord. By IT administration of MSC-

[3] Bensimon, G. et al., Riluzole Study Group, 1994. A controlled trial of riluzole in amyotrophic lateral sclerosis. *New England Journal of Medicine*, 330(9), pp585–591.
[4] Zoccolella, S. et al., 2007. Riluzole and amyotrophic lateral sclerosis survival: a population-based study in southern Italy. *European Journal of Neurology,* 3, pp262-268.
[5] Henriques, A. et al., 2010. Neurotrophic Growth Factors for the Treatment of Amyotrophic Lateral Sclerosis: Where Do We Stand? *Frontiers in Neuroscience,* 4, p32.
[6] Krakora, D. et al., 2012. Neuromuscular Junction Protection for the Potential Treatment of Amyotrophic Lateral Sclerosis. *Neurology Research International*, 2012, ID:379657, pp1-4.

NTF, the neurotrophic factors secreted by the transplanted cells are expected to be taken up by the axon cell bodies in the spinal cord and thus may better address pharmacokinetic concerns regarding NTF delivery time and delivery concentrations to motor neurons. Finally, Brainstorm has differentiated MSC to secrete several neurotrophic factors including glial derived neurotrophic factor (GDNF) and brain derived neurotrophic factor (BDNF). Each of these neurotrophic factors has been shown to be beneficial in animal models of ALS.[5]

The successful completion of Phase I/II clinical trials has provided initial confirmation that the treatment is safe and also some indications of beneficial clinical effects. This suggests that MSC-NTF could be a potential treatment for ALS. In January of this year, the Israeli Ministry of Health approved the acceleration of the study to Phase IIa. The progression to Phase IIa is intended to establish the effects of escalating dosage.

About BrainStorm Cell Therapeutics: More information on BrainStorm Cell Therapeutics can be found at http://www.lifesciadvisors.com/clients/brainstorm/.

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