BrainStorm Cell Therapeutics, Inc. (BCLI – OTC)

INITIATION

We are initiating coverage of BrainStorm Cell Therapeutics, Inc. (BCLI) with a Buy rating and a $0.50 price target. BrainStorm is developing adult stem cell therapies for the treatment of Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS), Parkinson’s disease (PD), and autism utilizing the company’s NurOwn™ technology, whereby autologous Mesenchymal Stem Cells (MSC) are differentiated into neurotrophic factor (NTF) secreting cells.

BrainStorm has recently initiated a randomized, double-blind, placebo controlled, Phase 2 trial in ALS in the U.S., with results expected in mid to late 2015. Additional upcoming catalysts include uplisting to a major exchange and advancement of an additional preclinical program into human clinical testing.

BrainStorm Cell Therapeutics, Inc.

BCLI: Initiating coverage of BrainStorm Cell Therapeutics, Inc….

Current Recommendation: Buy
Prior Recommendation: N/A
Date of Last Change: 06/11/2014
Current Price (06/11/14): $0.30
Target Price: $0.50

52-Week High: $0.31
52-Week Low: $0.24
One-Year Return (%): N/A
Beta: N/A
Average Daily Volume (sh): 634,846
Shares Outstanding (mil): 183
Market Capitalization ($mil): $56
Short Interest Ratio (days): N/A
Institutional Ownership (%): 0
Insider Ownership (%): N/A

Annual Cash Dividend: $0.00
Dividend Yield (%): 0.00

5-Yr. Historical Growth Rates
Sales (%): N/A
Earnings Per Share (%): N/A
Dividend (%): N/A

P/E using TTM EPS: N/A
P/E using 2013 Estimate: N/A
P/E using 2014 Estimate: N/A

Risk Level: Above Average
Type of Stock: Small-Growth
Industry: Med-Biomed/Gene

ZACKS ESTIMATES

Revenue (In millions of $)

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Earnings per Share
(EPS is operating earnings before non-recurring items)

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Initiating Coverage

We are initiating coverage of BrainStorm Cell Therapeutics, Inc. (BCLI) with a Buy rating and a $0.50 price target.

BrainStorm is a biotechnology company developing adult stem cell therapies for a range of neurodegenerative diseases, including Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS), and Parkinson's disease (PD), along with neurodevelopment disorders including autism. The company has a proprietary process called NurOwn™ that harvests and propagates autologous Mesenchymal Stem Cells (MSC) and then induces their differentiation into neurotrophic factor (NTF) secreting cells, called MSC-NTF. BrainStorm then returns the cells to the patient at or near the target area for treatment. Because these cells are autologous, there is very little risk of rejection or tumor formation.

Neurotropic factors are secreted proteins that promote neuron growth, differentiation, and survival both in vivo and in vitro. They were first identified as survival factors for sympathetic and sensory neurons and are now known to control a number of aspects of survival, development and function of neurons. They are required throughout life, as they control synaptic function and plasticity and sustain neuronal cell survival, morphology, and differentiation. Examples include Glial-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and hepatocyte growth factor (HGF).

BrainStorm believes that its MSC-NTF cells possess a number of characteristics that will provide utility for the treatment of neurodegenerative diseases. These include their ability to:

- Protect existing neurons,
- Promote motor neuron growth,
- Re-establish nerve-muscle interactions.

In addition, as these cells are autologous (derived from the patient being treated) there is no risk for rejection and no need to use immunosuppressive agents. Since these are adult stem cells, the technology is free from the ethical concerns surrounding the use of embryonic stem cells.

BrainStorm recently initiated a Phase 2 clinical trial in ALS patients using NurOwn™ cells. This is a multi-center, randomized, double blind, placebo controlled trial that will evaluate the safety and efficacy of a single combined intramuscular and intrathecal administration of MSC-NTF cells in early-stage ALS patients. The trial is expected to enroll 48 patients randomized 3:1 to receive either NurOwn™ cells or placebo. Trial results are expected in mid-to-late 2015.

BrainStorm recently hired Tony Fiorino, MD, PhD as the Chief Executive Officer (CEO). Dr. Fiorino has extensive experience in the biopharmaceutical industry as an investor, entrepreneur, and drug developer. He has previously served as the manager of a healthcare equity fund, a consultant to biotechnology and pharmaceutical companies, and as CEO of EnzymeRx, where he led the development of a late-stage compound through a pair of clinical trials and the subsequent sale to 3SBio.

The company reported $3.0 million in cash and investments as of March 31, 2014. We believe BrainStorm will need to raise additional funds later in 2014 in order to fund the Phase 2 trial to completion. We estimate costs of the program are approximately $7 million to complete. In addition, the company is working on the requirements to allow them to uplist to a major exchange, most likely the NASDAQ. In support of this, BrainStorm has recently repurchased outstanding warrants originally issued in the company’s August 16, 2013 public offering. We believe an uplisting will occur before the end of 2014. The company will need to undertake a reverse split to meet minimum bid requirements for the NASDAQ Capital Markets exchange (i.e. $3 per share).
INVESTMENT THESIS

Stem Cells – A Quick Background

Stem cells are distinguished from other types of cells in the body due to their unique characteristics: the capacity of self-renewal, their undifferentiated state, and their ability to differentiate into specialized cell types. These qualities make them especially attractive from a therapeutic standpoint.

- **Self-renewal capabilities:** Unlike heart, muscle, or nerve cells (which typically do not replicate, or make copies of themselves), stem cells are capable of replicating many times, otherwise known as proliferating. Starting with a population of stem cells in the laboratory, long-term proliferation of that population will result in millions of identical cells.

- **Undifferentiated state:** Stem cells do not express any factors or have any tissue-specific structures that allow them to perform specialized functions. For example, stem cells will not contract in rhythm together like a group of cardiomyocytes (heart muscle cells).

- **Differentiation potential:** The process by which unspecialized cells give rise to specialized cells is known as differentiation. Typically, a cell goes through a series of several steps during the process of differentiation based on both external and internal signals. As an example, bone marrow contains hematopoietic stem cells, which are capable of giving rise to the many different types of blood cells.

Stem cells are capable of developing into many different cell types and also serve as an internal repair system by dividing without limit to replenish other cells. In some organs, such as the gut and bone marrow, stem cells regularly divide to repair and replace old or damaged tissue while in other organs, such as the heart and pancreas, stem cells only divide under special conditions. There are two mechanisms by which stem cells:

- **Obligatory asymmetric replication:** The process by which a stem cell divides into two cells, with the original stem cell dividing into a mother cell that is identical to the original, and a daughter cell that is differentiated.

- **Stochastic differentiation:** The process by which one stem cell develops into two differentiated daughter cells, which a second stem cell divides into two stem cells that are identical to the original.

The differentiation potential of stem cells is indicated by the potency. Not all stem cells have the same potency, with some stem cells being able to differentiate into any cell type while others can only differentiate into a limited number of cell types. The potency classifications are as follows:

- **Totipotent:** The “most potent” of stem cells that are found just after an egg is fertilized by a sperm. These cells could theoretically form a complete organism.

- **Pluripotent:** Immediate descendants of totipotent stem cells that can differentiate into most types of tissues except the placenta.

- **Multipotent:** Cells that can differentiate into many different types of cells, but only those that belong to the same “family”. For example, hematopoietic stem cells can develop into several different types of blood cells (red blood cells, platelets, lymphocytes, etc.) but can’t develop into nerve cells or muscle cells.

- **Oligopotent:** Can differentiate into a very limited number of closely related cells. For example, vascular stem cells can become either endothelial cells or smooth muscle cells.

- **Unipotent:** Have the capacity to produce only one type of cell, however they have the property of self-renewal that distinguishes them from non-stem cells.
Different Types & Uses of Stem Cells...

There are three different types of stem cells:

- **Embryonic stem cells (ESC):** These cells are derived from embryos that have been fertilized in vitro. They are isolated from the inner cell mass of blastocysts (4-5 day old embryos) and have the capacity to develop into over 200 different cell types. Changing the chemical composition of the culture medium in which they are grown can control differentiation and different cell types can be derived through this procedure. Due to the way they are isolated, which involves the destruction of a human embryo, there is considerable controversy surrounding their use. In addition, embryonic stem cells carry the risk of developing into teratoma's (an encapsulated tumor) if they are not correctly differentiated following injection.

- **Adult stem cells (ASC):** These cells are found among the differentiated cells of an organ or tissue and are capable of differentiating to become some or all of the specialized cell types of that organ or tissue. The primary role of adult stem cells is to maintain or repair the tissue in which they are found. The different types of adult stem cells identified thus far include: Hematopoietic, which give rise to all the types of blood cells; Mesenchymal, which give rise to a variety of cell types including bone, cartilage, and fat; Neural, which give rise to the three major cell types in the brain; Epithelial, which give rise to several different cell types in the digestive tract; Skin, which give rise to the keratinocytes and the epidermis.

- **Induced pluripotent stem cells (iPSC):** These are adult cells that have been genetically reprogrammed to an embryonic stem cell-like state by the forced expression of genes and factors important for maintaining and defining the properties of embryonic stem cells. While they meet the defining criteria for pluripotent stem cells, at the current time it is not known if iPSCs and ESCs will differ in clinically significant ways.

**...BrainStorm's Technology...**

BrainStorm’s NurOwn™ technology is based on a novel differentiation protocol that induces differentiation of bone-marrow derived mesenchymal stem cells (MSCs) into neuron-supporting cells (MSC-NTF) capable of releasing elevated levels of several different neurotrophic factors, including Glial-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and hepatocyte growth factor (HGF). All of these factors are critical for the growth, survival, and differentiation of developing neurons.

MSCs are multipotent adult stem cells that can be isolated from a number of different tissues, including umbilical cord blood, adipose tissue, adult muscle, corneal stroma, bone marrow, and the developing tooth bud of the mandibular third molar. Bone marrow derived MSCs are one of the main sources of MSCs and are the source for the cells used in BrainStorm’s therapy. Morphologically, MSCs are long and thing with a small cell body containing a large, round nucleus.

Based on the different methods of isolation and expansion, along with different ways of characterizing MSCs, the International Society for Cellular Therapy has suggested the following minimal criteria to define human MSCs (Dominici et al., 2006):

- MSCs must be plastic-adherent when grown under standard cell culture conditions.
- MSCs must express the surface markers CD105, CD73, and CD90; they must lack expression of CD45, CD34, CD14 or CD11b, CD79a or CD19, and HLA-DR surface markers.
- MSCs must differentiate into osteoblasts, adipocytes, and chondroblasts in vitro.

**Neurotrophic factors** are secreted proteins that promote neuron growth, differentiation, and survival both in vivo and in vitro (Skaper 2012). They were first identified as survival factors for sympathetic and sensory neurons and are now known to control a number of aspects of survival, development, and function of neurons. They are required throughout life, as they control synaptic function and plasticity and sustain neuronal cell survival, morphology, and differentiation.
The process by which bone marrow derived MSCs are converted to MSC-NTF cells involves removal of a bone marrow sample from a patient through bone marrow aspiration, followed by isolation of the MSCs. These MSCs are first cultured in a proprietary growth medium and then induced to differentiate using a medium-based approach in the presence of growth factors and reagents to induce secretion of Neurotrophic factors. These MSC-NTF cells are then transplanted back into the patient's spinal cord or muscles.

After the culturing process is complete, the cells can be stained to confirm that they are expressing the proper neurotrophic factors. This is shown in the following image where both MSC and MSC-NTF cells were stained with a nucleus staining reagent (blue) and an antibody directed towards either GDNF or BDNF, with the antibody containing a fluorescent marker that can be visualized using fluorescence microscopy (green). The images show that normal MSC cells do not express neurotrophic factors but after progressing through BrainStorm's proprietary differentiation protocol the cells now express the neurotrophic factors GDNF and BDNF.

Once the cells are confirmed to be expressing neurotrophic factors, they are reintroduced into the same patient from whom the original bone marrow sample was taken. This autologous or self-transplanted approach using the patient's own stem cells removes the risk of rejection that can occur through allogenic therapy, which is the use of cells from another individual. The use of the patient's own stem cells also eliminates the need for immunosuppressive agents that can have multiple side effects including an increased risk of infection, hypertension, and liver/kidney damage. Since the MSC-NTF cells are adult stem cells, there are also no ethical considerations found with the use of embryonic stem cells.

The ability to induce differentiation of autologous stem cells before transplantation is a unique advantage of the NurOwn™ technology. The neurotrophic factors are important due to their ability to 1) protect existing motor neurons, 2) promote motor neuron growth, and 3) re-establish nerve-muscle interactions.
When the stem cells are transplanted back into the patient they are administered via intrathecal and/or intramuscular injection. An intrathecal injection is made directly into the spinal canal, specifically the subarachnoid space, such that it reaches the cerebrospinal fluid. It is performed with a standard lumbar puncture (otherwise known as a spinal tap), and does not require an invasive surgical procedure such as a laminectomy. This is one advantage of BrainStorm’s MSC-NTF cells vs. Neuralstem’s NSI-566. Neuralstem’s procedure with NSI-566 requires direct injection into the exposed spinal cord. Intramuscular injections are performed with a standard injection procedure as well and thus far have been performed in the bicep and triceps muscles. The advantage of intramuscular injections is that if the company is able to show efficacy, for instance if an ALS patient who can’t move their fingers or arm is able to after MSC-NTF intramuscular treatment, it could offer a complimentary treatment alternative.

**Clinical Indication I: Amyotrophic Lateral Sclerosis**

BrainStorm is targeting the neurodegenerative disease Amyotrophic Lateral Sclerosis (ALS) for treatment with MSC-NTF cells. ALS is a debilitating disease that affects nerve cells in the brain and spinal cord and there is currently no known cure.

**...Background on ALS...**

ALS is a rapidly progressing neurodegenerative disease whereby the nerve cells in the brain and spinal cord that control muscle movement degenerate. This rapid degeneration of the motor neurons eventually leads to death, typically in three to five years after patients are first diagnosed. As the motor neurons cease to function properly, they can no longer send signals to the muscle fibers, and thus voluntary muscle action is progressively affected. Eventually, patients in later stages of the disease may become completely paralyzed which includes losing the ability to control their breathing. In the U.S., approximately 30,000 people are currently living with ALS.

Early symptoms of ALS include increasing muscle weakness or stiffness, especially involving the arms and legs. Additional signs of the disease may include difficulty swallowing, cramping, and/or slurred speech. The specific set of neurons that are first affected by the disease dictates what portion of the body will be affected first. Approximately 75% of patients experience “limb onset” ALS. This means they first notice symptoms in their arms and legs. Patients with leg symptoms typically experience difficulty when walking or running, and they may have a tendency to trip or stumble more often. Those patients with arm symptoms may first notice difficulties with buttoning a shirt, opening a can, or writing. The other 25% of cases are “bulbar onset” ALS. These patients first notice difficulty with speaking, swallowing, or their speech. Up to one third of ALS patients may experience “pseudobulbar effect”, a neurological disorder with consists of the inability to control certain emotions, such as laughing and crying, which is due to the degeneration of bulbar upper motor neurons.

As the disease progresses all patients will eventually experience increased difficulty swallowing and speaking, with most patients not able to walk or use their arms or hands. The rate at which this occurs varies from patient to patient and is measured utilizing a scoring system called the “ALS Functional Rating Scale Revised” (ALSFRS-R). This scoring system consists of a series of 12 questions on basic tasks (speech, salivation, swallowing, handwriting, cutting food, dressing and hygiene, turning in bed, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency) that are rated on a five-point scale where 0 = can’t do and 4 = normal ability. The individual items are summed to produce a score of between 0 = worst and 48 = best.

For the majority of ALS patients (~95%) there is no known cause of the disease. A very small number of cases can be attributed to a genetic component where ALS is known to run in families (familial ALS). Of these familial cases, approximately 20% are associated with a defect in the gene that encodes superoxide dismutase (SOD1), with over 100 different SOD1 mutations described thus far. It is unknown exactly how mutations in SOD1 lead to neuron degeneration; however, a leading theory is that mutations in superoxide dismutase cause the protein to misfold and aggregate inside the cell. Aggregated proteins are a common pathological feature of both familial and sporadic ALS, and a mouse model of ALS, where the mice harbor a mutation in Sod1, showed aggregated protein accumulated only in diseased tissue (Furukawa et al., 2006).

Interestingly, mice that lack the Sod1 gene entirely do not normally develop ALS, although they do tend to exhibit age-related muscle atrophy and a shortened lifespan. These data together suggest that the properties of mutant SOD1 are not due to a loss of function but rather a gain of function brought on by the mutation.
There are only a limited number of treatment options available for ALS patients. Sanofi's Riluzole® (rilutek) is the only treatment shown to improve survival, but only for two to three months. The compound works by preferentially blocking tetrodotoxin (TTX)-sensitive sodium channels that are associated with damaged neurons (Song et al., 1997). This prevents influx of calcium ions and indirectly prevents stimulation of glutamate receptors. Together with direct glutamate receptor blockade, the effect of the neurotransmitter glutamate on motor neurons is greatly reduced. Rilutek does not reverse damage already done to motor neurons, and people taking it must be monitored for liver damage (approximately 10% incidence). Sales of Riluzole® peaked at around $50 million per year. It is now available as a generic.

The remaining treatments for ALS are designed to relieve symptoms and improve quality of life. This supportive care includes a multidisciplinary approach that may include medications to reduce fatigue, control spasticity, reduce excess saliva and phlegm, limit sleep disturbances, reduce depression, and limit constipation.

...BrainStorm’s ALS Therapy...

BrainStorm is developing a therapy for ALS using their NurOwn™ technology and the transplantation of MSC-NTF cells that they believe will protect existing motor neurons, promote motor neuron growth, and aid in re-establishing nerve-muscle interactions. BrainStorm has conducted a Phase 1/2 safety trial with the MSC-NTF cells, is currently in the follow-up stage of a Phase 2a dose-escalating trial in Israel, and has recently enrolled the first patient a Phase 2 clinical trial at multiple centers in the U.S. We discuss these programs below.

Phase 1/2 Clinical Trial

A Phase 1/2 non-randomized, open label, safety, and tolerability trial was conducted at Hadassah Medical Center in Jerusalem between June 2011 and Dec. 2012. This trial was performed with Principal Investigator Professor Dimitrios Karussis and consisted of 12 ALS patients classified according to their ALSFRS-R score; six patients who were early stage (ALSFRS-R score > 30) and received intramuscular (IM) injections (at 24 separate sites on the biceps and triceps muscles) and an additional six patients who were progressive stage (ALSFRS-R score of 15-30) and received intrathecal (IT) injections. The patients treated with IM injections received a total of 24 million cells, while those treated with IT injections received 1 million cells per Kg of body weight. A general timeline for the trial is indicated below.

![General Timeline](image)

Importantly, BrainStorm was able to show the elevated levels of NTFs secreted by the MSC-NTF cells of the patients in this study, as compared to the levels of NTFs secreted by their MSCs, as shown in the following graphs. The blue bars represent the amount of GDNF, BDNF, VEGF, or HGF detected from the patients' MSC cells before differentiation, while the red bars are the amount detected after differentiation into MSC-NTF cells.
Professor Karussis presented results of the trial at the March 2013 American Academy of Neurology Annual Meeting. The study met its primary endpoints of safety and tolerability, with no treatment-related adverse events reported in the 12 patients. In addition, some clinical improvements were noted in IT-treated patients. There was a slower decline in overall clinical and respiratory function as measured by the ALSFRS-R and Forced Vital Capacity (FVC) score when comparing the three months pre-treatment with the six months following treatment, as shown in the figures below.

The p values in the above graphs below each of the lines on the graphs represent the difference in respective scores from the first time point to the last for the three months before treatment (orange line) and the six months after treatment (purple line). For example, the change in the ALSFRS-R score between time points 1 and 4 is statistically different (p = 0.005), whereas the change in ALSFRS-R score between time points 4 and 10 is not statistically different (p = 0.90). A similar pattern held true for FVC scores as well. In addition, there was a statistically significant difference in the differences between time periods (before vs. after treatment) for both ALSFRS-R score (p = 0.0013) and FVC score (p < 0.001). What these results indicate is that the treatment appears to be slowing the rate of decline in both ALSFRS-R and FVC scores. While these results are still preliminary and involve only a small group of patients, they are still encouraging, as the course of ALS is unpredictable, and may be stable in some patients even for extended periods, but typically runs in a constant decline, with no evident improvement in the patients' condition.
Phase 2a Clinical Trial

Following on the success of the Phase 1/2 clinical trial, BrainStorm initiated a Phase 2a prospective, open label, dose-escalating clinical trial. This trial was also conducted at the Hadassah Medical Center in Jerusalem and was initiated in January 2013. The protocol originally called for 12 early-stage ALS patients to receive both IM and IT injections of NurOwn™ cells in three cohorts with increasing doses between February and August 2013. Just as for the Phase 1/2 trial, eligible patients were observed for 3 months prior to treatment to determine the progressive rate of disease with the patients followed for six months after transplantation. The first treatment cohort received a total dose of 94 million cells, the second cohort received 141 million cells, and the final cohort received 188 million cells (based on average patient weight of 70 kg).

The primary endpoint of the Phase 2a trial is safety and tolerability of a single, combined treatment of MSC-NTF cells administered both IM and IT at the three different dosing levels. There are a number of secondary endpoints, which include changes in the progression rate of the disease as evidenced by changes in the ALSFRS-R score, FVC, changes in muscle strength, changes in muscle bulk, changes in upper and lower extremities circumference, and changes in EMG parameters. All patients will be monitored on a monthly basis for six months following treatment for safety and potential signs of efficacy.

BrainStorm announced they had completed treatment of 12 ALS patients in the Phase 2a study in September 2013. An interim safety summary for the 12 treated patients was produced two months after the final patient was dosed and it reported one death due to cardiopulmonary arrest, which was confirmed as non-treatment related. In addition, in the three months following the interim safety report, one patient chose to undergo euthanasia and was removed from the study. Furthermore, due to an unexpected technical issue related to cell proliferation in two patients, two additional patients were enrolled in the trial in late 2013 and dosed in the first quarter 2014, bringing the total number of treated patients to 14.

Interim results from the trial were presented by Principal Investigator Professor Dimitrios Karussis at the Joint Congress of European Neurology on June 1, 2014. Prof. Karussis summarized the results from both ALS trials, and presented an interim analysis of the data for the first 10 out of 14 patients in the current Phase IIa trial. In all 26 patients who received NurOwn™ in the two trials, no treatment-related serious adverse events were observed. In the three-month pre-treatment “run-in” period, 71% of the patients showed progression of disease with decline in neurological function. In contrast, in the three months post-transplantation with NurOwn™, 63% of the patients who received intrathecal (IT), or combined IT and intramuscular (IM) administration, showed stabilization or improvement in neurological function, as measured by their revised ALS functional rating score (ALSFRS-R). According to Prof. Karussis, these differences in the preliminary analysis were statistically significant at p=0.035, chi-square test.

Additionally, as Professor Karussis mentioned in his presentation, 63% of the patients treated with NurOwn™ via IT or combined IT and IM administration were defined as “responders” (slower progression of disability or improvement in their neurological function) at 3 months post-treatment, based on both their ALSFRS-R and FVC scores. The six patients treated with NurOwn™ in the earlier Phase 1/2 trial via IM administration only, primarily exhibited a localized positive effect. Similarly, in the same Phase 1/2 trial, the IT transplanted patients also showed indications of neurotrophic and regenerative effects, as evidenced by an increase in Compound Muscle Action Potential (CMAP) in the treated arm. The complete and final statistical analysis of the Phase 2a trial should be available in the fourth quarter of 2014.

Phase 2 Clinical Trial in U.S.

On April 28, 2014, BrainStorm announced FDA approval for the commencement of a Phase 2 clinical trial (NCT02017912) in the U.S. with NurOwn™ cells for the treatment of ALS. This is a multi-center, randomized, double blind, placebo controlled trial that will evaluate the safety and efficacy of a single combined IM and IT administration of MSC-NTF cells in early-stage ALS patients. Just as with the other studies, patients will be assessed for three months before treatment and then will be followed for six months after treatment. The trial is expected to enroll 48 patients randomized 3:1 to receive either NurOwn™ cells or placebo. BrainStorm just recently enrolled the first patient in early June 2014.

The primary endpoint is safety based on the number of patients with adverse events. Secondary endpoints include the change in ALSFRS-R and slow vital capacity (SVC) slopes. Just as in prior studies, the change in slopes will be compared before and after treatment.
The trial will take place at three centers in the U.S.: Massachusetts General Hospital (MGH), University of Massachusetts Memorial Hospital, and the Mayo Clinic. The Dana Farber Cancer Institute’s Connell O’Reilly Cell Manipulation Core Facility will manufacture the NurOwn™ cells for both MGH and UMass Memorial. The Mayo Clinic’s Human Cell Therapy Laboratory will manufacture the NurOwn™ cells for the trial there. The fact that the FDA approved a Phase 2 trial in the U.S. without requiring a Phase 1 trial is encouraging, and speaks to the positive safety profile seen thus far in the other clinical trials testing NurOwn™ treatment.

…Case Study of NurOwn™ Treatment…

A report was published in the journal Muscle and Nerve in March 2014 that showed the potential for MSC-NTF treatment. A 75-year-old patient who was previously diagnosed with myasthenia gravis (MG) and ALS was allowed treatment with MSC-NTF cells based on a special license on a compassionate basis given by the Hadassah Ethics Committee. The patient was treated with both intrathecal (1.5 x 10^6 cells per kg body weight) and intramuscular (1 x 10^6 cells per site) injections at 24 sites along the biceps and triceps muscles of the right arm. One month after transplantation the patient and his family reported significant improvement in cognition, speech, and muscle power. In addition, the patient was able to walk at least 20 meters without support after having been confined to a wheelchair before the procedure.

At six months post-transplantation a repeat injection of MSC-NTF cells was performed due to progression of weakness and deterioration in cognition. On the patients last examination two months after the second transplantation all neurological functions had improved significantly. ALSFRS-R score rose from 30 to 43 (note 48 is “perfect score”), muscle power improved significantly, and FVC increased. The following graph shows the change in ALSFRS-R score for the patient over time.

While very few definitive conclusions can be drawn from the case study of one patient, it still is quite exciting that the ALSFRS-R score increased so dramatically after each administration of MSC-NTF cells, and improvements in speech and muscle strength were also noted for this individual. While we would not expect every patient to respond in this way, these results do offer some insight into the possibilities of MSC-NTF treatment.

…Market Opportunity…

ALS is diagnosed in approximately 5,600 people in the U.S. every year and there are an estimated 30,000 patients who are currently living with the disease. With the cost to care for a patient with advanced stage disease estimated to be as high as $200,000, this represents a direct cost of more than $6 billion each year to the healthcare system.

As mentioned previously, there are very limited treatment options for patients with ALS. Riluzole is the only FDA approved medication shown to slow the progress of ALS. It acts by reducing nerve damage and may extend the time before a patient needs a ventilator and could prolong a patient's life by several months. Prior to loss of patent exclusivity, Riluzole® costs around $12,000 per year and had sales peak in 2012 of $50 million. This suggests that around 4,200 ALS patients were taking Riluzole® in 2012, or around 15% of the entire U.S. ALS population. Both baclofen and diazepam are used to control muscle spasms, stiffness, or tightening that interfere with daily activities. Trihexyphenidyl and amitriptyline are used to treat patients who have excess saliva and secretions as well as emotional changes. None of the aforementioned drugs alters the course of the diseases.
ALS is a highly complex disease that has multiple pathways of degeneration. Previous ALS drug development efforts have typically focused on one specific mechanism of action, and those have largely been met with failure. BrainStorm’s approach using autologous stem cells provides multiple means by which to confer a therapeutic effect and we believe it has a much better chance of showing a clinically meaningful benefit to patients.

Given the limited treatment options and high costs associated with patient care, we believe a treatment that altered progression of the disease would command a premium price, possibly as high as $100,000 per patient. The FDA granted NurOwn™ Orphan Drug designation in February 2011 with the European Commission granting Orphan Medicinal Product designation in July 2013.

Clinical Indication II: Multiple Sclerosis

In addition to the clinical work being conducted with ALS, BrainStorm is working on expanding the capabilities of the NurOwn™ technology by focusing on additional applications. Multiple sclerosis is one such indication, as it is another neurodegenerative disorder that affects the brain and spinal cord.

Multiple sclerosis (MS) is a chronic autoimmune, inflammatory disease that affects axons in the central nervous system (CNS). Axons are long, slender projections of nerve cells (neurons) that conduct electrical impulses that transmit information to different neurons, muscles, and glands. Axons are typically insulated with a protective sheath called myelin, which facilitates the proper conductance of nerve signals. When the myelin sheath is damaged there is interference in the communication between the brain, spinal cord, and other areas of the body. This process may also lead to the deterioration of the nerve cells themselves, a condition that is not reversible.

There is no single diagnostic test for MS, with diagnosis based on the following criteria: 1) at least two different lesions in the white matter of the CNS, 2) at least two different episodes in the disease course, and 3) chronic inflammation of the CNS as determined by analysis of the cerebrospinal fluid (CSF). Having one or more of these criteria allows a general diagnosis of MS.

The pattern and course of the disease is characterized by the following patterns:

- **Primary progressive:** Characterized by disease progression from the onset with occasional plateaus and temporary minor improvements. It makes up approximately 10 percent of cases at onset. Patients typically experience a steady decline in function from the beginning and never have acute attacks.

- **Relapsing remitting:** Relapsing-remitting MS is characterized by clearly defined relapses with full recovery. There is no disease progression during the periods between relapses. This type of MS accounts for approximately 85 to 90 percent of MS cases at onset. However, most patients will then progress into secondary progressive phase.

- **Secondary progressive:** Characterized by an initial relapsing-remittance phase followed by progression with or without occasional relapses, minor remissions, and plateaus. Studies suggest that most patients with relapsing-remitting MS will go on to develop secondary progressive MS.

- **Progressive relapsing:** Characterized by progressive disease from the onset, with clear acute relapses, with or without full recovery. Disease progression continues to occur during the periods between disease relapses.
There are a host of symptoms associated with MS depending on the location of the affected nerves. Symptoms can include:

- **Optic neuritis**: The most common type of involvement of the visual pathways. It typically presents as acute eye pain that is followed by variable vision loss affecting mainly central vision.

- **Sensory symptoms**: These are common in almost every MS patient at some time during the course of the disease. Symptoms include decreased light touch perception, numbness, tingling, pins-and-needles, and swelling of the limbs or trunk.

- **Vertigo**: A relatively common symptom of MS as it is reported in approximately 30 to 50 percent of patients.

- **Tingling or pain in different parts of the body**: Pain is a common symptom in patients with MS, with many different types of pain reported such as dysesthetic pain (unpleasant, abnormal sense of touch), back pain, and Lhermitte’s sign (an electrical sensation that runs down the back and into the limbs).

- **Extreme fatigue**: Typically described as physical exhaustion that is unrelated to the amount of activity performed. Many patients complain of feeling exhausted when waking up, even after a good night's rest.

- **Bowel/bladder/sexual function**: It is very common for patients with MS to have problems with constipation, urinary incontinence, and sexual dysfunction.

- **Problems with memory or concentration**: Cognitive dysfunction is rare and is usually only encountered in severely affected individuals, however a larger number of MS patients have cognitive impairment that includes problems with abstract conceptualization, short-term memory, attention, and speed of information processing.

The cause of MS is currently unknown and has been the focus of great attention for more than half a century. The most widely accepted theory at this point states that MS begins as an inflammatory autoimmune disorder mediated by activated lymphocytes (Weiner, 2006). As the disease progresses, it is dominated by microglial (resident macrophages of the CNS) activation and chronic neurodegeneration (Compston et al., 2008).

Initially, the inflammation is transient and remyelination occurs but is not durable. This leads to those in the early phase of the disease having episodes of neurological dysfunction that usually resolves. However, over time widespread microglial activation occurs, leading to enhanced pathological changes that lead to a progressive accumulation of disability.

While there is a large amount of data supporting the notion that MS is an autoimmune disorder, direct proof of an autoimmune cause of the disease is lacking as no specific autoantibody or auto-reactive T-cell directed against a self-antigen in the nervous system can passively transfer MS to an experimental animal. The controversy surrounding the cause of MS has been debated for more than 50 years, and leads to articles such as the following that appeared back-to-back in the same issue of JAMA Neurology in 2004:

Epidemiological evidence supports the idea that there are certain risk factors for getting MS. One risk factor is sex, with the female to male ratio of MS incidence being approximately 2.3:1 (Alonso et al., 2008). The mean age of onset for the disease is 30 years of age, with the peak age of onset approximately five years earlier in women than in men. In support of a possible autoimmune basis for MS, some studies have shown that patients with MS are more likely to have other autoimmune disorders, such as autoimmune thyroid disease.
The incidence and prevalence of MS varies around the world. High frequency areas include Europe, southern Canada, northern U.S., New Zealand, and Australia. The prevalence in the U.S. is approximately 100 per 100,000, for a total of 250,000 people with MS. There are racial differences in the prevalence as well, which may explain the geographic differences, with white populations, especially those from Northern Europe, being the most susceptible. People of Asian, African, or American Indian origin have the lowest risk. Another possible explanation for the geographic differences in disease prevalence is that sunlight exposure may be protective, either due to an effect of ultraviolet radiation or vitamin D (Ascherio et al., 2007).

...Current Treatment Options for MS...

The goal of MS therapy is to shorten the duration of acute exacerbations, decrease their frequency, and provide symptomatic relief. There are no curative therapies currently available; however, there are nine FDA-approved therapeutic agents that can reduce disease severity and progression in patients with relapsing forms of MS, including patients who have secondary progressive MS and continue to have relapses.

✓ Beta interferons: There are four beta interferons – Avonex® (Biogen Idec), Rebif® (Pfizer), Betaseron® (Bayer), and Extavia® (Novartis). Beta interferons are naturally occurring cytokines secreted by immune cells that act by inhibiting viral replication via a variety of immunomodulating and antiviral activities. The mechanism of action is unknown, but their anti-inflammatory properties are thought to be beneficial.

✓ Glatiramer Acetate (Copaxone®): A synthesized copolymer polypeptide mixture consisting of L-glutamic acid, L-lysine, L-alanine, and L-tyrosine. It is recommended as a first line treatment for those patients who cannot tolerate beta interferons. The mechanism of action is unknown, but it appears to activate suppressor T-cells and reduce inflammatory activity.

✓ Mitoxantrone (Novantrone®): This is a potent inhibitor of topoisomerase II, an enzyme responsible for repairing damaged DNA. Previously used to treat certain cancers, mitoxantrone suppresses the activity of T cells, B cells, and macrophages that are thought to lead the attack on the myelin sheath.

✓ Natalizumab (Tysabri®): Natalizumab is a humanized monoclonal antibody, and like the beta-interferons its exact mechanism of action in MS patients has yet to be fully elucidated. It binds to the specific receptors on the surface of leukocytes and inhibits adhesion to their counter-receptors.

✓ Fingolimod (Gilenya®): Fingolimod is a sphingosine-1-phosphate receptor modulator that blocks migration of lymphocytes from lymph nodes, thereby reducing the number of lymphocytes in the blood. The therapeutic mechanism in MS patients is also unknown. Researchers believe it might involve the reduction of lymphocyte migration to the CNS.

✓ Dimethyl fumarate (Tecfidera®): DMF (formerly known as BG-12) is an orally administered immune modulator that was approved in March 2013 by the FDA. It appears to have both anti-inflammatory as well as neuroprotective effects. It is quickly becoming the standard of care for MS. The drug is sold by Biogen Idec.

...Pre-clinical Evidence of MSC-NTF Efficacy in MS...

BrainStorm has conducted pre-clinical studies in animal models of MS that have shown the therapeutic effects of MSC-NTF cells. Experimental autoimmune encephalomyelitis (EAE), the animal model for MS, is a T cell-mediated inflammatory disease with variable degrees of demyelination and axonal damage. The model is produced through immunization with myelin antigens such as myelin-oligodendrocyte glycoprotein and myelin basic protein. When those proteins are injected with adjuvant there is a CD4+ T helper cell response that attacks the myelinated areas of the CNS resulting in inflammation, demyelination, and neurodegeneration (Whitman et al., 1991).

In a 2009 study published in the Journal of Molecular Neuroscience, researchers showed that intracerebroventricular transplantation of human MSC-NTF cells attenuated the clinical symptoms of EAE mice (Barhum et al., 2009). The study utilized human MSCs derived from healthy donors, with the cells put through the proprietary two-step cell culture process to induce secretion of neurotrophic factors.

MSC differentiation to MSC-NTF cells was confirmed through both immunohistochemistry (the use of antibodies directed against specific neurotrophic factors to confirm the cells are producing those factors) and real-time PCR (to quantify the fold increase of neurotrophic factor expression). The following figure on the left shows the increase in expression for a range of neurotrophic factors following the differentiation protocol.
MSC-NTF cells were injected directly into the brains of mice six days after EAE induction with the mice developing acute EAE clinical signs 12 days after immunization. Mice were scored for clinical signs using a scale of 0-6, with 0 representing no paralysis and 6 representing death, with the numbers in between for increasing levels of paralysis. The above right figure shows that both MSCs and MSC-NTF cells offer a protective effect in EAE mice, with MSC-NTF cells resulting in a slightly lower EAE clinical score and a statistically significant increase in longevity after induction of EAE.

...Market opportunity...

There are approximately 250,000 to 350,000 MS patients in the U.S. and over 2.5 million people with MS worldwide. There are over 10,000 new cases diagnosed annually in the U.S. Annual treatment costs for MS can be as much as $34,000 per year.

While there are a number of treatment options available for MS patients, there is currently no curative treatment with even the most effective treatments only able to slow the progression of the disease. We believe this creates an opportunity for therapeutics with unique mechanisms of action. NurOwn™ therapy for MS is still in the pre-clinical phase, thus we do not incorporate it into our valuation model. However, with strong pre-clinical data and a novel approach to treating the disease, it will be interesting to see whether this approach is efficacious for treating MS in a clinical setting.

Clinical Indication III: Parkinson's Disease

A third neurodegenerative disease that BrainStorm may target is Parkinson’s disease (PD), a chronic, progressive disorder that affects certain nerve cells in the brain. PD is a slowly progressing neurological disorder characterized by tremor, stiffness, decreased movement, and postural instability affecting approximately 0.4% of the population over age 40 and 1% of those over age 65 (Merck Manual). The disease arises from the death of dopamine-generating cells in the substantia nigra region of the midbrain, believed by many to be in association with the accumulation of a protein called alpha-synuclein in neurons. The disease is named after the English doctor James Parkinson, who published the first detailed description in An Essay on the Shaking Palsy in 1817.

The earliest symptoms of the disease include tremor, typically of a single hand or foot while at rest. Tremors may become less prominent and rigidity more prominent as the disease progresses. Over time, the patient finds it more difficult to initiate movement (akinesia) and movement generally becomes slower (bradykinesia) and reduced in amplitude. Muscle pain and fatigue are common in association with these symptoms. The face eventually becomes masklike with open mouth and drooling, and speech becomes unclear and difficult to initiate. Postural instability becomes more prominent as the disease progresses, resulting in difficulty walking and maintaining balance. Without warning, voluntary movement may suddenly halt. Overall, patients with PD find it increasingly difficult to initiate and control movement as the disease progresses, leading to disability, isolation, and loss of independence. In the most advanced stages of the illness, increasing physical disability may be accompanied by a variety of other neurological symptoms, including insomnia, psychosis, and dementia.
There are no disease-modifying agents available for the treatment of PD. Instead, the goal of treatment is to reduce symptoms, which can often be maintained at manageable levels for many years. In the early stages of the disease, patients may be treated with dopamine agonists such as Mirapex™, which binds to and turns on dopamine receptors in the brain in a manner closely analogous to dopamine itself. Alternatively, monoamine oxidase inhibitors may be used. Monoamine oxidase plays an important role in the healthy brain by metabolizing dopamine and preventing its level from rising excessively. However, in the Parkinson's brain, inhibitors of this enzyme help offset the effect of reduced dopamine production.

As the disease progresses, treatment with MAO inhibitors or dopamine agonists are no longer sufficient to control symptoms and treatment with levodopa is initiated. Levodopa, discovered in the 1960's, is an amino acid derivative that enters the brain via specific amino acid transporters and is converted to dopamine by an enzyme called dopa decarboxylase (Hauser, 2009). The administration of levodopa temporarily diminishes the motor symptoms associated with the lack of dopamine in the substantia nigra. Unfortunately, only about 5-10% of levodopa crosses the blood-brain barrier. The remainder is often metabolized to dopamine elsewhere, causing a variety of side effects including nausea, dyskinesias, and joint stiffness.

In the 1970's, the dopamine decarboxylase inhibitor carbidopa was discovered. Carbidopa is an inhibitor of aromatic amino acid decarboxylation, an enzyme that breaks down levodopa in the periphery and converts it to dopamine. By inhibiting the breakdown of levodopa to dopamine outside of the brain, the addition of carbidopa reduces the amount of levodopa required to produce a given response by about 75% and, when administered with levodopa, increases both plasma levels and the plasma half-life of levodopa, and decreases plasma and urinary dopamine. A combination levodopa/carbidopa formulation called SINMET CR is available in the U.S. This approach helps to reduce some of the side effects of dopamine therapy, but does not slow disease progression or inhibit dyskinesia, nausea, hallucinations, and other psychiatric disorders from developing.

**Pre-clinical Evidence of MSC-NTF Efficacy in PD...**

There is a significant unmet need for novel approaches to the treatment of PD, primarily to control levodopa-induced adverse side effects and motor dysfunction, as well as to delay the onset of disease-related dementia. In support of this, a number of pre-clinical studies have been performed with MSC-NTF cells in animal models of PD. The most widely used animal model of PD involves the use of 6-hydroxydopamine (6-OHDA), a highly specific neurotoxin that targets catecholamine neurons via the dopamine active transporter (Torres et al., 2012). When it is injected into the brain, it causes extensive, irreversible loss of dopamine neurons.

A 2009 study showed protective effects of MSC-NTF cells in a 6-OHDA rat model of PD (Sadan et al., 2009). Human MSC and MSC-NTF cells were injected into the brains of rats treated with 6-OHDA to determine their protective effects. Damage to the brains was assessed by examining the activity of tyrosine hydroxylase, an enzyme expressed in dopamine producing neurons.

The figure below shows that MSC-NTF cells (C) were able to protect more neurons compared to buffer (A) or MSC cells (B), as judged by tyrosine hydroxylase staining (brown).

![Source: Sadan et al., 2009](image)

In addition, the study demonstrated that the injected cells migrated from their original injection site, raising the possibility that the cells would be able to migrate to the site of injury. In the following figure, iron oxide particles can be seen in a control treated animal (A) at the sight of cell injection (blue circle), with very little seen at the sight of 6-OHDA injection (red circle). However, in animals treated with MSC-NTF cells loaded with iron oxide particles (B), there is a clear migratory pathway that can be seen going from the cell transplantation site (blue circle) to the 6-OHDA lesion site (red arrow).
...Market potential...

There are an estimated 6.3 million people worldwide that suffer from PD, with approximately one million in the U.S. (PDF.org) The market for pharmaceuticals to treat PD is estimated at $2.4 billion per year in the U.S., France, Germany, Italy, Spain, the U.K., and Japan. The National Parkinson's foundation estimates the total economic burden of the disease to exceed $14 billion annually in the U.S. alone. This includes the costs of medical treatment, caring, facilities and other services, as well as loss of productivity of both patients and caregivers. With few treatment options and no curative therapies available, there is a clear unmet medical need for PD patients to have access to more effective treatment options. BrainStorm is continuing pre-clinical studies with MSC-NTF cells as a treatment for PD, thus we will not account for this application in our valuation model.

Clinical Indication IV: Autism

A final neural development disease that BrainStorm is targeting is autism. Autism is a set of neurodevelopment conditions that are characterized by severe deficits in socialization, communication, and repetitive or unusual behaviors. Autism is one of the three recognized autism spectrum disorders (ASDs), with the other two being Asperger syndrome, which lacks delays in cognitive development and language, and pervasive developmental disorder, not otherwise specified, which is diagnosed when the full set of criteria for autism or Asperger syndrome are not met. In order to be diagnosed with autism, a child needs to develop symptoms before the age of three.

The conditions are most likely caused by a complex interaction between genetic and non-genetic risk factors. Epidemiological studies have identified various risk factors; however, none have proven to be necessary or sufficient alone for autism to develop. Advanced maternal or paternal age is a consistent risk. The underlying reason for this is unclear but may have to do with germline mutation (Sandin et al., 2012; Hultman et al. 2011). Gestational factors that could affect the pregnancy, such as exposure to chemicals (Christensen et al., 2013), has been suggested to increase the risk for autism while folic acid supplementation both before and during early pregnancy seems to be protective (Suren et al., 2013).

The prevalence of autism appears to be increasing since the first epidemiological study was conducted in the 1960’s. The reasons for this are unclear but are most likely due in part to the result of changes in diagnoses and criteria (Fisch, 2012). However, the prevalence has continued to rise the past two decades, especially in individuals without intellectual disability (Keyes et al., 2012). Whatever the reason, improved awareness and recognition along with changes in diagnosis and a younger age of diagnosis are also contributory factors.

More than 70% of individuals with autism have concurrent medical, developmental, or psychiatric conditions, with more co-occurring conditions present leading to an increase in the patient's disability. In fact, patients with autism have a mortality risk that is 2.8 times higher than that of a similar population of unaffected people, however this increased risk is almost solely due to co-occurring medical conditions (Bilder et al., 2013).

The transition to adulthood is difficult for most autism patients. For this reason, early intervention to try to slow or halt the disease is important, with early identification being critically important to begin treatment as early in life as possible. Previously, children with autism were not identified until they were older than 3-4 years old, however now toddlers are frequently diagnosed due to atypical development being recognized early on.
The goals of intervention are to maximize an individual's functional independence and quality of life through development and learning, improvements in social skills and communication, reductions in disability and comorbidity, and promotion of independence.

There are currently no drugs that have been reliably shown to improve social communication in autistic patients. Antipsychotic drugs (such as risperidone and aripiprazole) have been shown to effectively reduce challenging and repetitive behaviors in children with autism; however, there is a risk for adverse side effects (McPheeters et al., 2011). Non-traditional therapies such as melatonin, vitamins, and gluten-free diets are most likely not harmful, but their effectiveness is not established (Akins et al., 2010).

…Market potential…

According to the Centers for Disease Control, autism spectrum disorders are identified in approximately 1 in 68 children, with the condition almost five times more common among boys (1 in 42) than among girls (1 in 189). The cost of treatment and care for individuals with ASD in the U.S. is approximately $137 billion annually, making it a significant public health problem (Knapp et al., 2012).

BrainStorm is beginning pre-clinical work in a mouse model of autism to explore the effects of the company’s NurOwn™ technology on mouse behavior. The initial study will examine repetitive behavior, increased cognitive flexibility, and improved sociability in mice after administration of a single intracerebroventricular injection of MSC-NTF cells. Stem cell therapy has been proposed as a treatment for autism, as the cells may affect molecular processes associated with autism pathophysiology.

VALUATION AND RECOMMENDATION

We are initiating coverage of BrainStorm Cell Therapeutics, Inc. (BCLI) with a Buy rating and a price target of $0.50. We believe that BrainStorm's NurOwn™ technology holds meaningful potential, and while the amount of clinical data generated to date has been limited, we like what we have seen thus far and are anxiously awaiting future clinical data, specifically in ALS.

…A Novel Stem Cell Technology…

BrainStorm is a biotechnology company developing adult stem cell therapies for a range of neurodegenerative diseases, including Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS), and Parkinson's disease (PD). The company has a proprietary process called NurOwn™ that harvests and propagates autologous Mesenchymal Stem Cells (MSC), and then induces their differentiation into Neurotrophic factor (NTF) secreting cells called MSC-NTF cells. BrainStorm then returns the cells to the patient at or near the target area for treatment. Because the cells are autologous, there is very little risk of rejection or tumor formation.

BrainStorm’s NurOwn™ technology is based on a novel differentiation protocol that utilizes MSC-NTF cells capable of releasing several different neurotrophic factors, which are secreted proteins that promote neuron growth, differentiation, and survival. When the stem cells are transplanted back into the patient they are administered via intrathecal and/or intramuscular injection. An intrathecal injection is made directly into the spinal canal, specifically the subarachnoid space, such that it reaches the cerebrospinal fluid. It is performed with a standard lumbar puncture (otherwise known as a spinal tap), and does not require an invasive surgical procedure such as a laminectomy. Intramuscular injections are performed with a standard injection procedure as well and thus far have been performed in the bicep and triceps muscles. The advantage of intramuscular injections is that if the company is able to show efficacy, for instance if an ALS patient who can't move their fingers or arm is able to after MSC-NTF intramuscular treatment, it could offer a complimentary treatment alternative.
…Opportunity in ALS…

While there has not been an enormous amount of clinical data generated thus far, we are encouraged by what we have seen. In the Phase 1/2 clinical trial in ALS, the company was able to show that the NurOwn™ process successfully generated MSC-NTF cells from the MSC cells taken from patients, with some patients showing a slowing of disease progression when comparing the six months post-transplantation with the three months pre-transplantation.

Similar results have been seen in the interim data from the Phase 2a trial, where 63% of patients who received intrathecal or combined intrathecal and intramuscular administration showed stabilization or improvement in neurological function, as measured by the ALSFRS-R (p = 0.035). BrainStorm has recently enrolled the first patient in a double-blind, placebo controlled Phase 2 clinical trial in the U.S., and based upon the results reported thus far from the Phase 1/2 and 2a trials, we are excited to see how the trial in the U.S. turns out.

We have constructed a sales model for NurOwn™ in ALS that assumes a U.S. filing in 2019 and approval in 2020. NurOwn™ treatment will not be one-time treatment but will require repeated administration of cells, which we are currently estimating at once every four months, or three times per year. The company will need to perform clinical trials to determine the optimum time frame for repeated administration of MSC-NTF cells, however the case report described earlier reported a second transplantation of cells approximately five months after the first injection. Thus, we believe that a four month window is a good estimate at this juncture.

We are calculating a fair value for BrainStorm based on an applied price-to-sales (P/S) multiple. We estimate peak sales will occur in 2025. By then, we forecast there will be approximately 34,000 ALS patients in the U.S. We estimate that 50% of these patients will be unsuitable for treatment, due to the fact that they have bulbar ALS or are too far advanced in their disease for the treatment to be successful (ALSFR < 15). This leaves approximately 17,000 ALS patient’s eligible for NurOwn™ therapy. Clinical efficacy of NurOwn™ treatment will ultimately dictate the uptake amongst patients; however, we have estimated a 30% peak market penetration, noting that this could likely range anywhere from 5% if the drug has limited effectiveness to 75% or higher if the drug is highly effective. We forecast NurOwn™ to cost $40,000 per treatment, or $120,000 per year. This leads to peak revenues of approximately $900 million.

Biotechnology companies are typically valued on price-to-sales, with the industry average being anywhere from 4-6x. We apply a 5x sales multiple on our peak 2025 revenue assumption and discount this back to the present with a 25% discount rate. We also assume only a 30% chance of success based on the fact that the treatment has just started Phase 2 trials. This leaves us with a fair value of approximately $120 million. Dividing by a fully diluted share count of 247.5 million shares we arrive at a fair value of approximately $0.50.

…A Nice Risk/Reward Profile...

With a current market cap of approximately $50 million, we view the stock as having a favorable risk/reward profile. Buyers today would have limited downside should the Phase 2 trial yield less than optimal results. However, there is a potentially large upside should the data come back better than expected. In addition, the use of intramuscular administration opens the door for targeted treatments, for instance in trying to get arm/hand/finger movement restored to an ALS patient for the purposes of using a fork or holding a cup. While we have not modeled this opportunity specifically, we will certainly re-evaluate this opportunity should the clinical data indicate this as a future application.

Another way to look at BrainStorm’s valuation is to compare it to another stem cell company, both in terms of their mechanism of action as well as their market value. Neuralstem (CUR) is developing a treatment for ALS using human neural stem cells that both help create new circuitry and express factors that protect existing cells. The neural stem cells are injected directly into the grey matter of a patient’s spinal cord, a much more invasive procedure than the simple intramuscular or intrathecal administration that BrainStorm uses.

Neuralstem currently has a market cap of approximately $400 million compared to approximately $50 million for BrainStorm, with fully diluted market caps of approximately $600 million and $70 million, respectively. While Neuralstem is ahead of BrainStorm in the clinic, with Neuralstem anticipating beginning a registration trial in 2015, we do not believe that warrants Neuralstem having a market cap right times that of BrainStorm. A direct comparison between the two companies is somewhat complicated by the fact that Neuralstem also has a novel small molecule discovery program aimed at altering neuronal cells in addition to stem cell therapy. Neuralstem is also pursuing spinal cord injury and stroke with its cell therapy.
Again, we don't feel that this is enough to warrant such a large difference in value between the two companies. We believe the market is underappreciating the simplicity of BrainStorm's approach, and that both increased exposure and continued evidence of clinical efficacy will help to drive BrainStorm's stock price higher and more in line with Neuralstem's.

Stem cell treatment is not necessarily a zero sum game in the treatment of ALS. We can foresee how a patient may opt for treatments from both Neuralstem and BrainStorm, particularly in regards to the targeted intramuscular treatments that BrainStorm is investigating in the clinic. Thus, even if Neuralstem were to come out with fantastic results from their ALS clinical trial, we would not view that as a complete loss for BrainStorm as we do not believe that would necessarily exclude NurOwn™ treatment from the market.

Lastly, we have not included in our valuation model the application of NurOwn™ technology in Parkinson's disease, multiple sclerosis, or autism, as these programs are all pre-clinical. However, we view these programs as decreasing the investment risk as BrainStorm will not be solely dependent upon the application of NurOwn™ to ALS as these pre-clinical programs are advanced into the clinic.

### RISKS

#### Potential Risks to our thesis

- **Stem cell therapy fails.** While we are encouraged by the results we have seen thus far, it is important to point out that the NurOwn™ technology is still early stage, and has only been tested in 26 patients thus far in clinical trials, thus there is no guarantee that BrainStorm will be successful. In addition, any potential therapeutic application will require multiple administrations of cells, something that BrainStorm has not yet tested in the clinic outside of the case report discussed earlier in the report. Even with the dramatic results reported in the case study, there is no guarantee that repeated administrations of cells will be tolerated by patients or will be effective.

- **Repeat administrations of NurOwn™ cells will be necessary, potentially making the treatment untenable for patients and/or insurance companies.** BrainStorm is not claiming that the NurOwn™ treatment will be a one time event, but instead will require repeat administrations at yet to be determined time intervals. Clinical trials will need to be performed to understand the optimum time frame and amount of treatment for repeat administrations. While unlikely due to the fact there are few if any treatment options for ALS patients, repeat treatments could potentially cause insurance companies to hold back coverage, particularly if repeated administrations result in a significant yearly cost. This would also be dependent upon just how efficacious the treatment is.

- **Other stem cell therapeutics are more efficacious than NurOwn™.** Neuralstem (CUR) is developing a stem cell treatment for ALS using neural stem cells that are injected directly into the patient's spinal column. There have been anecdotal reports of some patients experiencing dramatic improvements in their disease during the Neuralstem clinical trials. In addition, Neuralstem will most likely be starting a Phase 3 registration trial in 2015, thus they are further ahead in development than BrainStorm. While we don't necessarily view ALS stem cell therapy as a zero sum game, treatments that are first to market do have an advantage. One way in which BrainStorm has mitigated this risk is by also testing NurOwn™ as a targeted treatment through injections directly into the biceps and triceps. Thus, even if Neuralstem's treatment ends up being more efficacious overall, there could still be an opportunity for using NurOwn™ as a targeted complimentary treatment.

- **BrainStorm will need to raise a significant amount of money that could result in shareholder dilution.** The company will need to raise additional funds to support the Phase 2 clinical trial in the U.S. and continued development of the pre-clinical programs. While BrainStorm has been successful in the past at raising money, there is no guarantee that they will be able to do so in the future or that it would be come at favorable terms for the company and current shareholders.
MANAGEMENT PROFILES

Tony Fiorino, M.D., Ph.D. – Chief Executive Officer
Dr. Fiorino has a broad and extensive experience in the biopharmaceutical industry as an investor, entrepreneur, and drug developer. Prior to joining BrainStorm, he helped manage a healthcare equity fund as well as serving as a consultant to biotechnology and pharmaceutical companies. Previously, Dr. Fiorino was Founder, President, and CEO of EnzymeRx, a company that acquired a late-stage, pre-clinical biologic, where he led the development of the compound through a pair of clinical trials and subsequent sale to 3SBio. Before founding EnzymeRx, Dr. Fiorino worked as a biotechnology and pharmaceutical analyst and portfolio manager at firms including JP Morgan, Citigroup, and Pequot Capital. Dr. Fiorino earned an M.D. and a Ph.D. from the Albert Einstein College of Medicine, where he studied the differentiation of liver progenitor cells, and a B.S. from the Massachusetts Institute of Technology.

Chaim Lebovits – President
Chaim Lebovits has been at the forefront of mining and natural resource management in African regions for over a decade. Mr. Lebovits is the Chairman and CEO of ACC Holdings International, an Investment Company with several holdings in gas fields, gold mines, and biotech. Mr. Lebovits has invested to date more than $5 million dollars in BrainStorm. As President of the company since July 2007, he has played an active role in its strategic planning and development on an ongoing basis.

Liat Sossover – Chief Financial Officer
Ms. Sossover has more than 14 years of experience as a financial officer in a wide range of international companies. Ms. Sossover previously served as Vice President of Finance for ForeScout Technologies and as VP of Finance and Secretary of Maximal Innovative Intelligence, which was acquired by Microsoft. Ms. Sossover has held positions as Chief Financial Officer at RT Set, which is now part of Vizrt and Financial Controller for BVR Technologies, which later was acquired by Esterline Technologies. Ms. Sossover has an MBA from Edinburgh University, and a Bachelor’s degree in Accounting & Economics from Ben Gurion University.

Yael Gothelf, Ph.D. – Vice President, Scientific and Regulatory Affairs
Dr. Gothelf has over fifteen years’ experience in the biotechnology industry. At BrainStorm she is responsible for regulatory compliance, clinical trials, product development and intellectual property. Before joining the company in 2007, she was the Scientific Manager of the Research and Process Development Division of InterPharm Laboratories, Israel a subsidiary of Ares-Serono. Prior to that, she was a Researcher at the Molecular and Cell Biology Department of the Weizmann Institute of Science, where she also completed her post-doctorate fellowship. Dr. Gothelf holds a PhD from Tel Aviv University.

Yossef Levy, Ph.D. – Vice President, Cell Production
As a member of the original Tel Aviv University research team that developed the NurOwn™ technology, Dr. Levy has been a core member of BrainStorm’s R&D team since the inception of the company. He is also responsible for the company’s in-house cGMP production for clinical trials, technology transfer, and training to U.S.-based cleanroom facilities, and co-development of bioreactor-based production scale-up. In addition, Dr. Levy supervises the company’s cleanroom operations and management, logistical coordination and personnel training. He received an MHA in Health Systems Management and a Ph.D. in Neurobiology from Tel Aviv University, as well as an M.Sc. in Clinical Pharmacy from Hebrew University. He is a licensed pharmacist.

Eldad Melamed, M.D. – Chief Medical Advisor
Prof. Melamed is a world-renowned expert in the field of neurodegenerative diseases, particularly on Parkinson’s disease. Prof. Melamed has served as head of the Neurology Department at the Rabin Medical Center and Tel Aviv University since 1987. Throughout his career, he has specialized in neurology, holding senior positions at the Hebrew University (Jerusalem), Bispebjerg Hospital (Copenhagen), National Hospital (London) and at the Laboratory of Neuroendocrine Regulation (Massachusetts). He is a past president of the Israel Neurological Association and former director of the National Parkinson Foundation (USA). Prof. Melamed is a member of the Scientific Committee of the Michael J. Fox Foundation for Parkinson’s Research. Prof. Melamed is a co-inventor named in the NurOwn™ technology patent.

Daniel Offen, Ph.D. – Chief Scientific Advisor
Prof. Offen enjoys an internationally recognized reputation in neuroscience research. Since 1993 he has been head of the Neuroscience Laboratory at Tel Aviv University School of Medicine. He has lectured extensively, both at Tel Aviv University and international scientific conferences, and has supervised many Ph.D. students. Dr. Offen has published over 100 original scientific papers and several patents. Dr. Offen is a member of the Scientific Committee of the Israel Society for Neuroscience and a co-inventor named in the NurOwn™ technology patent.
## PROJECTED FINANCIALS

### BrainStorm Cell Therapeutics, Inc.
**Income Statement**

<table>
<thead>
<tr>
<th>BrainStorm Cell Therapeutics</th>
<th>2013 A</th>
<th>Q1 A</th>
<th>Q2 E</th>
<th>Q3 E</th>
<th>Q4 E</th>
<th>2014 E</th>
<th>2015 E</th>
<th>2016 E</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MSC-NTF Stem Cells</strong></td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td><strong>Total Revenues</strong></td>
<td>$0.0</td>
<td>$0.0</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td><strong>YOY Growth</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Cost of Goods / Services</strong></td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
<td>$0.0</td>
<td>$0.0</td>
<td>$0.0</td>
</tr>
<tr>
<td><strong>Product Gross Margin</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>R&amp;D</strong></td>
<td>$2.9</td>
<td>$0.7</td>
<td>$0.7</td>
<td>$0.8</td>
<td>$0.9</td>
<td>$3.1</td>
<td>$3.5</td>
<td>$4.0</td>
</tr>
<tr>
<td><strong>% R&amp;D</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>SG&amp;A</strong></td>
<td>$2.1</td>
<td>$0.4</td>
<td>$0.5</td>
<td>$0.5</td>
<td>$0.6</td>
<td>$2.0</td>
<td>$2.5</td>
<td>$3.0</td>
</tr>
<tr>
<td><strong>% SG&amp;A</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Operating Income</strong></td>
<td>($5.0)</td>
<td>($1.0)</td>
<td>($1.2)</td>
<td>($1.3)</td>
<td>($1.5)</td>
<td>($5.0)</td>
<td>($6.0)</td>
<td>($7.0)</td>
</tr>
<tr>
<td><strong>Net Other Income</strong></td>
<td>$0.1</td>
<td>($1.1)</td>
<td>($0.1)</td>
<td>($0.1)</td>
<td>($0.1)</td>
<td>($0.1)</td>
<td>($1.4)</td>
<td>($1.5)</td>
</tr>
<tr>
<td><strong>Pre-Tax Income</strong></td>
<td>($4.9)</td>
<td>($2.1)</td>
<td>($1.3)</td>
<td>($1.4)</td>
<td>($1.6)</td>
<td>($6.4)</td>
<td>($7.5)</td>
<td>($8.7)</td>
</tr>
<tr>
<td><strong>Taxes</strong></td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td><strong>Tax Rate</strong></td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Net Income</strong></td>
<td>($4.9)</td>
<td>($2.1)</td>
<td>($1.3)</td>
<td>($1.4)</td>
<td>($1.6)</td>
<td>($6.4)</td>
<td>($7.5)</td>
<td>($8.7)</td>
</tr>
<tr>
<td><strong>Net Margin</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Reported EPS</strong></td>
<td>($0.03)</td>
<td>($0.01)</td>
<td>($0.01)</td>
<td>($0.01)</td>
<td>($0.01)</td>
<td>($0.03)</td>
<td>($0.04)</td>
<td>($0.04)</td>
</tr>
<tr>
<td><strong>YOY Growth</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Wt. Ave Shares Outstanding</strong></td>
<td>161.1</td>
<td>176.3</td>
<td>180.0</td>
<td>187.0</td>
<td>191.0</td>
<td>183.6</td>
<td>200.0</td>
<td>215.0</td>
</tr>
</tbody>
</table>

*Source: Zacks Investment Research, Inc.*

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## CONSOLIDATED BALANCE SHEETS

U.S. dollars in thousands  
(Except share data)

<table>
<thead>
<tr>
<th></th>
<th>March 31, 2014</th>
<th>December 31, 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unaudited</td>
<td>Audited</td>
</tr>
<tr>
<td><strong>ASSETS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current Assets:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cash and cash equivalents</td>
<td>3,027</td>
<td>3,503</td>
</tr>
<tr>
<td>Account receivable</td>
<td>792</td>
<td>910</td>
</tr>
<tr>
<td>Prepaid expenses</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td><strong>Total current assets</strong></td>
<td><strong>3,853</strong></td>
<td><strong>4,446</strong></td>
</tr>
<tr>
<td>Long-Term Assets:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prepaid expenses</td>
<td>13</td>
<td>22</td>
</tr>
<tr>
<td><strong>Total long-term investments</strong></td>
<td><strong>13</strong></td>
<td><strong>22</strong></td>
</tr>
<tr>
<td>Property and Equipment, Net</td>
<td>327</td>
<td>258</td>
</tr>
<tr>
<td><strong>Total assets</strong></td>
<td>4,193</td>
<td>4,726</td>
</tr>
<tr>
<td><strong>LIABILITIES AND STOCKHOLDERS' EQUITY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current Liabilities:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trade payables</td>
<td>326</td>
<td>228</td>
</tr>
<tr>
<td>Accrued expenses</td>
<td>1,034</td>
<td>877</td>
</tr>
<tr>
<td>Other accounts payable</td>
<td>247</td>
<td>227</td>
</tr>
<tr>
<td><strong>Total current liabilities</strong></td>
<td><strong>1,607</strong></td>
<td><strong>1,332</strong></td>
</tr>
<tr>
<td>Long-Term Liabilities:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warrants issued to investors</td>
<td>1,726</td>
<td>655</td>
</tr>
<tr>
<td><strong>Total long-term liabilities</strong></td>
<td><strong>1,726</strong></td>
<td><strong>655</strong></td>
</tr>
<tr>
<td><strong>Total liabilities</strong></td>
<td>3,333</td>
<td>1,987</td>
</tr>
<tr>
<td>Stockholders' Equity:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stock capital: (Note 6)</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Common stock of $0.00005 par value - Authorized: 800,000,000 shares at March 31, 2014 and December 31, 2013; Issued and outstanding: 176,803,587 and 176,263,587 shares at March 31, 2014 and December 31, 2013 respectively.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional paid-in-capital</td>
<td>55,370</td>
<td>55,138</td>
</tr>
<tr>
<td>Deficit accumulated during the development stage</td>
<td>(54,518)</td>
<td>(52,407)</td>
</tr>
<tr>
<td><strong>Total stockholders' equity</strong></td>
<td><strong>860</strong></td>
<td><strong>2,739</strong></td>
</tr>
<tr>
<td><strong>Total liabilities and stockholders' equity</strong></td>
<td>4,193</td>
<td>4,726</td>
</tr>
</tbody>
</table>
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