BRAINSTORM CELL THERAPEUTICS INC.
Form 10-K
March 27, 2014

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 10-K

x ANNUAL REPORT UNDER SECTION 13 OR 15(D) OF THE SECURITIES EXCHANGE ACT OF 1934

FOR THE FISCAL YEAR ENDED DECEMBER 31, 2013

¨ TRANSITION REPORT UNDER SECTION 13 OR 15(D) OF THE SECURITIES EXCHANGE ACT OF 1934

FOR THE TRANSITION PERIOD FROM _____ TO _____

COMMISSION FILE NUMBER 000-54365

BRAINSTORM CELL
THERAPEUTICS INC.
(Exact Name of Registrant as specified in its charter)

Delaware (State or other jurisdiction of incorporation or organization)	20-8133057 (I.R.S. Employer Identification No.)
605 Third Avenue, 34th Floor New York NY (Address of principal executive offices)	10158 (Zip Code)

Registrant's telephone number, including area code: (646) 666-3188

Securities registered under Section 12(b) of the Act: None

Securities registered under Section 12(g) of the Act:

Title of each class	**Name of each exchange on which registered**
Common Stock, $0.00005 par value	**OTC Markets Group**

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ¨ No x

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. Yes ¨ No x

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes x No ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files).
Yes x No ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of the registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ¨

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer ¨	Accelerated filer ¨	Non-accelerated filer ¨ (Do not check if a smaller reporting company)	Smaller reporting company x

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ¨ No x

The approximate aggregate market value of the voting and non-voting common equity held by non-affiliates of the issuer as of June 30, 2013 (the last business day of the registrant's most recently completed second fiscal quarter), was $25,010,064.

As of March 7, 2014, the number of shares outstanding of the registrant's common stock, $0.00005 par value per share, was 176,263,587.

DOCUMENTS INCORPORATED BY REFERENCE

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PART IV

PART I
SPECIAL NOTE

Unless otherwise specified in this annual report on Form 10-K, all references to currency, monetary values and dollars set forth herein shall mean United States (U.S.) dollars.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This annual report contains numerous statements, descriptions, forecasts and projections, regarding Brainstorm Cell Therapeutics Inc. and its potential future business operations and performance. These statements, descriptions, forecasts and projections constitute "forward-looking statements," and as such involve known and unknown risks, uncertainties, and other factors that may cause our actual results, levels of activity, performance and achievements to be materially different from any results, levels of activity, performance and achievements expressed or implied by any such "forward-looking statements." Some of these are described under "Risk Factors" in this annual report. In some cases you can identify such "forward-looking statements" by the use of words like "may," "will," "should," "could," "expects," "h "anticipates," "believes," "intends," "plans," "estimates," "predicts," "likely," "potential," or "continue" or the negative o terms or similar words. These "forward-looking statements" are based on certain assumptions that we have made as of the date hereof. To the extent these assumptions are not valid, the associated "forward-looking statements" and projections will not be correct. Although we believe that the expectations reflected in these "forward-looking statements" are reasonable, we cannot guarantee any future results, levels of activity, performance or achievements. It is routine for our internal projections and expectations to change as the year or each quarter in the year progresses, and therefore it should be clearly understood that the internal projections and beliefs upon which we base our expectations may change prior to the end of each quarter or the year. Although these expectations may change, we may not inform you if they do and we undertake no obligation to do so. We caution investors that our business and financial performance are subject to substantial risks and uncertainties. In evaluating our business, prospective investors should carefully consider the information set forth under the caption "Risk Factors" in addition to the other information set forth herein and elsewhere in our other public filings with the Securities and Exchange Commission ("SEC") .

Item 1. BUSINESS.

Company Overview

Brainstorm Cell Therapeutics Inc. ("we," "us," "our" or the "Company") is a biotechnology company developing novel adul stem cell therapies for debilitating neurodegenerative disorders such as Amyotrophic Lateral Sclerosis ("ALS", also known as Lou Gehrig's disease), Multiple Sclerosis ("MS"), and Parkinson's disease ("PD"). These diseases have limited treatment options and as such represent unmet medical needs.

We believe that NurOwn, our proprietary process for the propagation of Mesenchymal Stem Cells ("MSC") and their differentiation into NeuroTrophic factor-("NTF") secreting cells ("MSC-NTF"), and their transplantation at, or near, the site of damage, offers the hope of more effectively treating neurodegenerative diseases.

Our approach is considered safe based on our use of autologous cells, which are free of the risk of rejection and tumor formation. It is also free of the controversy associated with the use of embryonic stem cells in some countries.

Our core technology was developed in collaboration with prominent neurologist Prof. Eldad Melamed, former head of Neurology of the Rabin Medical Center and member of the Scientific Committee of the Michael J. Fox Foundation for Parkinson's Research, and expert cell biologist Prof. Daniel Offen of the Felsenstein Medical Research Center of Tel Aviv University.

Our wholly-owned Israeli subsidiary, Brainstorm Cell Therapeutics Ltd. (the “Israeli Subsidiary”), holds rights to commercialize the technology, through a licensing agreement with Ramot at Tel Aviv University Ltd. (“Ramot”), the technology transfer company of Tel Aviv University, Israel.

On February 8, 2010, our Israeli Subsidiary entered into an agreement with Hadasit Medical Research Services and Development Ltd., a subsidiary of the Hadassah Medical Organization (“Hadassah”), pursuant to which Hadassah provides the Israeli Subsidiary with lab services.

On February 17, 2010, our Israeli Subsidiary entered into an agreement with Hadassah and Professor Dimitrios Karussis (the “Clinical Trial Agreement”). Under the Clinical Trial Agreement, Hadassah and our personnel agreed to conduct a clinical trial to evaluate the safety and tolerability of our NurOwn cells in patients with ALS, in accordance with a protocol developed jointly by us and Professor Karussis.

In February 2011, the U.S. Food and Drug Administration (“FDA”) granted Orphan Drug designation to NurOwn for the treatment of ALS.

In June 2011, we initiated a Phase I/II clinical trial for the treatment of ALS with NurOwn at the Hadassah University Medical Center in Jerusalem ("HUMC") with Principal Investigator Professor Dimitrios Karussis, after receiving approval from the Israeli Ministry of Health ("MoH").

In July 2011, we entered into a Memorandum of Understanding with Massachusetts General Hospital ("MGH") and the University of Massachusetts Medical School ("UMass") in anticipation of applying for FDA approval to begin ALS human clinical trials in the United States. In March 2014, we entered into a definitive agreement with MGH in order to launch a Phase II clinical trial in the second quarter of 2014, and we expect to enter into a definitive agreement with UMass for the same.

In July 2012, together with Professor Karussis, we submitted an interim safety evaluation report to the Israeli MoH for the first 12 of 24 patients in the Phase I/II clinical trial. The report confirmed that our NurOwn therapy is safe, did not cause any adverse side effects, and some of the patients showed promising indications of clinical improvement.

In January 2013, the Israeli MoH approved acceleration to a Phase IIa combined treatment, dose-escalating trial, which we are currently conducting at HUMC. According to the protocol for this safety and preliminary efficacy trial 12 early-stage ALS patients received both intramuscular and intrathecal injections of NurOwn cells in three cohorts with increasing doses between February and August 2013. The patients were followed for six months after transplantation. Due to medical and technical considerations, two additional patients were enrolled in the trial in late 2013, in order to preserve the originally planned protocol design. These two patients will be treated by the end of the first quarter of 2014. The complete and final statistical analysis of the Phase IIa data is expected to be available after 6 months of follow up with the patients.

In January 2013, we also announced that we had successfully completed a 12-week repeat dose toxicity study with our NurOwn cells in mice. These repeat doses were prepared from frozen cells, using a proprietary method recently developed by the Company. We believe that our cryopreservation, or freezing, method will enable long-term storage, and production of repeat patient doses of NurOwn without the need for additional bone marrow aspirations. We believe that the positive data from the toxicity study in mice will support our efforts to obtain approval for a future repeat dose clinical study in ALS patients. The study was conducted at Harlan Israel's laboratories, according to Good Laboratory Practice ("GLP") standards of the FDA. The study protocol was approved by Israel's National Council for Animal Experimentation.

In March 2013, Principal Investigator Professor Dimitrios Karussis of Hadassah presented some of the data from the Phase I/II trial at the American Academy of Neurology Annual Meeting. The trial results analyzed to date confirmed the safety of the NurOwn Treatment and also demonstrated initial signs of possible efficacy. There was a slower decline in overall clinical and respiratory function, as measured by the ALS Functional Rating Score ("ALSFRS-R") and Forced Vital Capacity ("FVC") score respectively, in the six patients that received an intrathecal injection of the cells, in the six months following treatment as compared to the three months preceding treatment.

On March 14, 2013, we entered into a Memorandum of Understanding with the Mayo Clinic ("Mayo") in Rochester, Minnesota, to participate as an additional clinical site in the multi-center Phase II ALS clinical trial in the USA. The team there will be led by Professor Anthony J. Windebank, Head of the Regenerative Neurobiology Laboratory in the Department of Neurology. In January 2014 we announced that we had entered into a definitive agreement with Mayo to conduct the trial and manufacture NurOwn cells in their cleanroom facility.

On April 3, 2013, we entered into a manufacturing agreement with Dana-Farber Cancer Institute ("Dana-Farber") under which Dana-Farber's Connell and O'Reilly Cell Manipulation Core Facility will produce NurOwn in its cGMP-compliant clean rooms for the MGH and UMass clinical sites during our upcoming Phase II ALS clinical trial in the United States.

In June 2013, we entered into a Memorandum of Understanding ("MOU") with PRC Clinical, a Contract Research Organization ("CRO") based in the San Francisco Bay Area, in anticipation of our planned Phase II multi-center ALS clinical trial in the United States.

On July 17, 2013, we received Orphan Medicinal Product Designation for our NurOwn for the treatment of ALS from the European Commission.

On August 1, 2013 we announced that we submitted a favorable safety report to the hospital Helsinki Committee (IRB) for the second group of patients in our ongoing Phase IIa ALS clinical trial at the Hadassah Medical Center in Jerusalem, Israel. We announced that the treatment was well tolerated and no serious adverse events were observed. Except for one SAE (Serious Adverse Event, death due to cardiopulmonary arrest) that was reported as non-treatment related.

On September 27, 2013 we announced that we had completed treatment of the 12 patients in our ALS Phase IIa NurOwn dose-escalating clinical trial. We have been informed that one patient in the study expired due to a medical condition unrelated to the Clinical Trial.

In October 2013, we announced that we launched our activities in the US in preparation for our Phase IIa multi-center clinical trial, with the initiation of the NurOwn technology transfer process at the Dana Farber Cancer Institute (DFCI). Since then, a series of on-site training sessions for cell manufacturing are ongoing at DFCI.

On December 10, 2013, we announced that Prof. Karussis presented some of his preliminary findings from our ALS Phase IIa NurOwn dose-escalating clinical trial at the 24th International Symposium on ALS/MND the previous week in Milan, Italy. According to Prof. Karussis, the safety data are "impressively positive," with only minimal and transient adverse events, even though the patients in this study were injected both intrathecally and intramuscularly with up to double the dose of NurOwn cells given in the Phase I trial. In addition, a number of patients showed some initial indications of clinical improvement.

In December 2013 the Company submitted an Investigational New Drug (“ IND”) application to the FDA.

Our Proprietary Technology

Our NurOwn technology is based on a novel differentiation protocol which induces differentiation of the bone marrow-derived mesenchymal stem cells into neuron-supporting cells, MSC-NTF cells, capable of releasing several neurotrophic factors, including Glial-derived neurotrophic factor (“GDNF”) and Brain-derived neurotrophic factor (“BDNF”), Vascular endothelial growth factor (VEGF) and Hepatocyte growth factor (HGF) which are critical for the growth, survival and differentiation of developing neurons.
GDNF is one of the most potent survival factors known for peripheral neurons. VEGF and HGF have been reported to have important neuro-protective effects in ALS.

Our approach to treatment of neurodegenerative diseases with autologous adult stem cells includes a multi-step process beginning with harvesting of undifferentiated stem cells from the patient's own bone marrow, and concluding with transplantation of differentiated, neurotrophic factor-secreting mesenchymal stem cells (MSC-NTF) into the same patient intrathecally and/or intramuscularly. Intrathecal (injection into the cerebrospinal fluid) transplantation consists of injection with a standard lumbar puncture; there is no need for a laminectomy an invasive, orthopedic spine operation to remove a portion of the vertebral bone, as required by other technologies. Intramuscular (injection directly into muscle) transplantation is performed via a standard injection procedure as well.

Our proprietary, production process for induction of differentiation of human bone marrow derived mesenchymal stem cells into differentiated cells that produce NTF (MSC-NTF) for clinical use is conducted in full compliance with current Good Manufacturing Practice (“cGMP”).

Our proprietary technology is licensed to and developed by our Israeli Subsidiary.

The NurOwn Transplantation Process

- Bone marrow aspiration from patient;
- Isolation and expansion of the mesenchymal stem cells;
- Differentiation of the expanded stem cells into neurotrophic-factor secreting (MSC-NTF) cells; and
- Autologous transplantation into the patient’s spinal cord or muscle tissue.

Differentiation before Transplantation

The ability to induce differentiation of autologous adult mesenchymal stem cells into MSC-NTF cells *before* transplantation is unique to NurOwn, making it the first-of-its-kind for treating neurodegenerative diseases.

The specialized cells secrete neurotrophic factors for:

- § Protection of existing motor neurons;
- § Promotion of motor neuron growth; and
- § Re-establishment of nerve-muscle interaction.

Autologous ("Self-transplantation")

The NurOwn approach is autologous, or self-transplanted, using the patient's own stem cells. In autologous transplantation there is no risk of rejection and no need for treatment with immunosuppressive agents, which can cause severe and/or long-term side effects. In addition, it is free of controversy associated with the use of embryonic stem cells in some countries.

Transplantation site and method

Clinical Indication I: ALS (current) Based on the approval of the Israeli MoH, we are currently conducting a Phase IIa dose-escalating trial to evaluate safety and preliminary efficacy of NurOwn in ALS patients. Pending approval of our IND application to the FDA, we are planning to launch a Phase II clinical trial in the USA in the second quarter of 2014. We intend to conduct further Phase II/III repeat dose clinical trials of NurOwn.

Clinical Indication II: MS (future) Based on positive proof-of-concept results obtained at Tel Aviv University with MSC-NTF cells for MS, we are currently conducting a pre-clinical study for this disease at HUMC's SPF-grade animal laboratory in Jerusalem. The study was approved by the Institutional Animal Care and Use Committee (IACUC) of the Hebrew University.

History

The Company was incorporated under the laws of the State of Washington on September 22, 2000, under the name Wizbang Technologies, Inc. and acquired the right to market and sell a digital data recorder product line in certain states in the U.S. Subsequently, the Company changed its name to Golden Hand Resources Inc. On July 12, 2004, the Company entered into a research and license agreement with Ramot to acquire certain stem cell technology and decided to discontinue all activities related to the sales of the digital data recorder product. In November 2004, the Company changed its name from Golden Hand Resources Inc. to Brainstorm Cell Therapeutics Inc. to better reflect its new line of business in development of novel cell therapies for neurodegenerative diseases. In October 2004, the Company formed its wholly-owned subsidiary, Brainstorm Cell Therapeutics Ltd. in Israel. On December 18, 2006, the stockholders of the Company approved a proposal to change the state of incorporation of the Company from the State of Washington to the State of Delaware. The reincorporation was completed on December 21, 2006 through the merger of the Company into a newly formed, wholly-owned Delaware subsidiary of Brainstorm, also named Brainstorm Cell Therapeutics Inc. On February 19, 2013, the Israeli Subsidiary formed its wholly-owned subsidiary, Brainstorm Cell Therapeutics UK Ltd. in the United Kingdom (the “UK Subsidiary”).

Other Recent Developments

Public Offerings

On August 16, 2013, the Company closed a public offering of an aggregate of 23,529,411 units at a public offering price of $0.17 per unit, with each unit consisting of one share of our common stock, and 0.75 of a warrant to purchase one share of our common stock at an exercise price of $0.25 per whole share of common stock (the "Warrants"). The Warrants are immediately exercisable and will expire three years from the issuance date. No units were issued, however, and purchasers received only shares of common stock and Warrants. The common stock and the Warrants may be transferred separately immediately upon issuances. We do not intend to list the Warrants on any securities exchange or other trading market and we do not expect that a public trading market will develop for the Warrants. The total expenses of this Offering were approximately $700,000. We have also reimbursed the underwriters for certain expenses. The net proceeds to the Company were approximately $3.3 million, assuming no exercise of the Warrants and after deducting the underwriting discounts and commissions and estimated offering expenses payable by us associated with the Offering.

On July 17, 2012, we raised approximately $5.7 million through a public offering (“2012 Public Offering”) of our common stock. We issued a total of 19,818,968 shares of our common stock at $0.29 per share and 14,864,228 warrants to purchase shares of common stock for every share purchased in the 2012 Public Offering, at an exercise price of $0.29 per share. The warrants are exercisable until the 30 month anniversary of the date of issuance. After deducting closing costs and fees, we received net proceeds of approximately $5 million.

Governmental Grants

In September 2011, we received notice from the Israeli Office of the Chief Scientist (“OCS”) of its commitment to grant the Company approximately $1.1 million in accordance with OCS guidelines and the relevant plan approved by the OCS (the “Approved Plan”).

In 2012, we received notices from the OCS of its commitment to grant the Company approximately $1,086,000 for the year ending June 30, 2013.

In December 2013, we were awarded an $800,000 non-dilutive grant from Israel’s Office of the OCS for the year 2014. In February 2014, we were awarded an additional $600,000 non-dilutive grant from the OCS for 2014.

With regards to any funding received from the OCS, we are obligated to pay royalties to the OCS, amounting to 3% to 3.5% of revenues (subject to the relevant regulations, as amended from time to time) derived from sales of the products funded with the OCS grant, depending on the origin of the products' production. Such royalty payments shall be up to an amount equal to 100% of the grant received. The grant is linked to the exchange rate of the U.S. dollar and bears interest of Libor per annum.

Any plan approved by the OCS research committee for grant funding is subject to Israel's Encouragement of Industrial Research and Development Law, 5744 1984 ("R&D Law"), which, among others, restricts the transfer of any know-how (as further defined therein) and the transfer of the manufacture of the outcome product of such Approved Plan outside of Israel.

The research committee may, in special cases, approve the transfer abroad of know-how or any right thereof, derived from research and development conducted under the Approved Plan in Israel, in exchange for receiving know-how from the party abroad; provided, however, that such exchange is towards joint and new research and development.

The research committee may, in special cases and on grounds to be recorded, approve a request to transfer outside of Israel, the manufacturing or the rights to manufacture a product developed within the framework of the Approved Plan; provided, however, that in exchange for such approval, the OCS shall be entitled to, *inter alia*, payment of increased royalties due to the transfer of such manufacturing rights.

Collaboration with Octane Biotech

On December 10, 2012, we signed a development agreement (the "Octane Agreement") with Octane Biotech Inc. of Kingston, Ontario ("Octane"), to jointly collaborate towards developing proprietary bioreactor for scale up production of our NurOwn treatment. The customized bioreactor (the "NurOwn Bioreactor") will enable us to enhance the efficiency of our NurOwn production process, significantly increasing our production capabilities by using a single clean room for multiple patients, reducing costs and time.

According to the Octane Agreement, in the event that the parties successfully complete the development of the NurOwn Bioreactor, the parties reserve the right to enter into an agreement for the supply of clinical products and/or provisions of services.

The Octane Agreement further dictates that Octane shall be prohibited from selling and/or transferring the NurOwn Bioreactor to any third party without our prior written consent.

The 3-year collaborative project with a total budget of 1,365,000 Canadian dollars is being supported by the Canada-Israel Industrial Research and Development Foundation which collaborates with the Israeli OCS. The Israeli OCS has confirmed its participation, in such project, of approximately U.S. $141,000 for the first year, which comprises 50% of our budget of approximately U.S. $282,000 for that period.
By the fourth quarter of 2013, Octane developed a first automation system prototype for culturing NurOwn cells, and for process development and optimization.

Development of Cryopreservation Method

In January 2013, we announced the development of a proprietary method for cryopreservation, or freezing, of cells, which will enable long-term storage, and production of repeat patient doses of NurOwn without the need for additional bone marrow aspirations. We believe that cryopreservation will enable us to create a personalized NurOwn stem cell bank for each patient, for ongoing, repeat treatments.

Orphan Drug Status by the European Medicine Agency ("EMA")

On July 17, 2013, we received Orphan Medicinal Product Designation for our NurOwn for the treatment of ALS from the European Commission. Orphan designation grants a 10-year marketing exclusivity in the EU for the designated indication, as well as several other regulatory incentives.

Clinical Trial Update

On September 27, 2013 we announced that we had completed treatment of 12 patients in our ALS Phase IIa NurOwn dose-escalating clinical trial. We have been informed that one patient in the study expired due to a medical condition unrelated to the Clinical Trial. An interim safety summary for the first 12 patients in the study was submitted to the Hadassah Medical Center Ethical Committee about two month after transplantation of the 12th patient. One SAE (Serious Adverse Event, death due to cardiopulmonary arrest) was reported as non-treatment related. The majority of the other AE observed were procedure related and not treatment related. In the three months following this summary, one patient chose to undergo euthanasia and discontinued the study.
Due to medical and technical considerations, two additional patients were enrolled in the trial in late 2013, in order to preserve the originally planned protocol design. These two patients will be treated by the end of the first quarter of 2014. The complete and final statistical analysis of the Phase IIa data is expected to be available after 6 months of follow up with the patients.

On December 10, 2013, we announced that Prof. Karussis presented some of his preliminary findings from our ALS Phase IIa NurOwn dose-escalating clinical trial at the 24th International Symposium on ALS/MND the previous week in Milan, Italy. According to Prof. Karussis, the safety data are "impressively positive," with only minimal and transient adverse events, even though the patients in this study were injected both intrathecally and intramuscularly with up to double the dose of NurOwn cells given in the Phase I trial. In addition, a number of patients showed some initial indications of clinical improvement.

Chief Executive Officer

On July 28, 2013, Alon Natanson, Chief Executive Officer of the Company, informed us of his resignation from his position with the Company effective 90 days after the notice. Mr. Natanson continued to hold the title of Chief Executive Officer of the Company until October 28, 2013, the end of the 90 day notice period required by Mr. Natanson's employment agreement. The Company is currently searching for a permanent Chief Executive Officer to replace Mr. Natanson.

On August 1, 2013, the Company appointed Chaim Lebovits, the President of the Company, as its Principal Executive Officer, and to assume the duties and responsibilities of the Chief Executive Officer on an interim basis while we search for a new Chief Executive Officer.

Our efforts are currently directed at:

- § Completing a Phase IIa dose-escalating clinical trial of NurOwn for the treatment of ALS with 14 ALS patients in Israel;

- § Conducting technology transfer of the NurOwn manufacturing process to the Dana Farber Cell culture facility DFCI in Boston and to the Mayo Clinic cell culture facility in Rochester;
- § Fulfilling all requirements for IND approval;
- § Obtaining IRB approval at the three U.S. clinical sites;
- § Initiating a Phase II ALS clinical trial of NurOwn in the United States;
- § Collaborating with Octane on development of a customized NurOwn bioreactor; and
- § Completing pre-clinical studies of NurOwn for the treatment of MS.

Stem Cell Therapy

Our activities are within the stem cell therapy field. Stem cells are non-specialized cells with a potential for both self-renewal and differentiation into cell types with a specialized function, such as muscle, blood or brain cells. The cells have the ability to undergo asymmetric division such that one of the two daughter cells retains the properties of the stem cell, while the other begins to differentiate into a more specialized cell type. Stem cells are therefore central to normal human growth and development, and also are a potential source of new cells for the regeneration of diseased and damaged tissue. Stem cell therapy aims to restore diseased tissue function by the replacement and/or addition of healthy cells by stem cell transplants.

Currently, two principal platforms for cell therapy products are being explored: (i) embryonic stem cells (“ESC”), isolated from the inner mass of a few days old embryo; and (ii) adult stem cells, sourced from bone marrow, cord blood and various organs. Although ESCs are the easiest to grow and differentiate, their use in human therapy is limited by safety concerns associated with their tendency to develop teratomas (a form of tumor) and their potential to elicit an immune reaction. In addition, ESC has generated much political and ethical debate due to the derivation of ESCs from aborted fetuses.

Cell therapy using adult stem cells avoids many of these concerns. Mesenchymal stem cells (“MSCs” are an example of adult stem cells. These “multi-potent” cells can produce more than one type of specialized cell of the body, such as bone, fat, cartilage, and other types of cells. They secrete factors that promote tissue repair, and decrease inflammatory and immune reactions. The bone marrow (“BM”) is an invaluable source of MSCs. Moreover, bone marrow may be obtained through a simple procedure of aspiration, from the patient himself, enabling autologous cell therapy, thus obviating the need for donor matching, circumventing immune rejection and other immunological mismatch risks, as well as avoiding the need for immunosuppressive therapy. We believe that autologous bone marrow-derived mesenchymal stem cells, which are capable of in-vitro growth and multipotential differentiation, are a preferable source of therapeutic stem cells.

Neurodegenerative Diseases

Studies of neurodegenerative diseases suggest that symptoms that arise in afflicted individuals are secondary to defects in neuron cell function and neural circuitry. To date, these diseases have been treated effectively with systemic drug delivery. Consequently, alternative approaches for treating neurodegenerative diseases have been attempted, such as transplantation of cells capable of replacing or supplementing the function of damaged neurons. For such cell replacement therapy to work, implanted cells must survive and integrate, both functionally and structurally, within the damaged tissue.

Amyotrophic Lateral Sclerosis (ALS)

ALS, often referred to as “Lou Gehrig's disease,” is a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord. Motor neurons reach from the brain to the spinal cord and from the spinal cord to the muscles throughout the body. The progressive degeneration of the motor neurons in ALS eventually leads to death. As motor neurons degenerate, they can no longer send impulses to the muscle fibers that normally result in muscle

movement. With voluntary muscle action progressively affected, patients in the later stages of the disease may become completely paralyzed. However, in most cases, mental faculties are not affected.

Approximately 5,600 people in the U.S. are diagnosed with ALS each year. It is estimated that as many as 30,000 Americans have the disease at any given time. Estimated annual treatment costs for advanced stage patients can be as high as $200,000, representing an aggregate direct cost to the healthcare system of more than $6 billion per year (Source: Alliance for Regenerative Medicine).

Early symptoms of ALS often include increasing muscle weakness or stiffness, especially involving the arms and legs, speech, swallowing or breathing.

ALS is most often found in the 40 to 70 year age group with the same incidence as MS. There appear to be more MS sufferers because MS patients tend to live much longer, some for 30 years or more. The life expectancy of an ALS patient averages about two to five years from the time of diagnosis. However, up to 10% of ALS patients will survive more than ten years.

Treatment decisions are typically determined by the patient's symptoms and the stage of the disease. Some medications used for ALS patients include:

- Riluzole - the only medication approved by the FDA to slow the progress of ALS. While it does not reverse ALS, Riluzole has been shown to reduce nerve damage. Riluzole may extend the time before a patient needs a ventilator (a machine to assist breathing) and may prolong the patient's life by several months;

- Baclofen or Diazepam - used to control muscle spasms, stiffness or tightening (spasticity) that interfere with daily activities; and

- Trihexyphenidyl or Amitriptyline used to treat patients who have excess saliva or secretions, and emotional changes.

Other medications may be prescribed to help reduce such symptoms as fatigue, pain, sleep disturbances, constipation, and excess saliva and phlegm.

Multiple Sclerosis (MS)

MS is a chronic neurodegenerative disorder that affects the brain and spinal cord. Nerve cells are normally insulated with a protective layer called myelin, which allows nerve signals to travel properly. In MS, the myelin is destroyed (demyelination), causing loss of function of the nerve cells and disrupting transmission of brain messages to various parts of the body. While generally thought to be an autoimmune disease, the exact cause of MS is unknown.

There are currently over 2.5 million people with MS worldwide, with roughly 800,000 of these in the U.S. and Europe. Over 10,000 new cases are diagnosed annually in the U.S., with the majority of these in women between the ages of 20 and 50. Annual treatment costs for MS can be as much as $34,000 a year per patient.

MS can cause blurred vision, slurred speech, tremors, numbness, extreme fatigue, and problems with memory and concentration. Most MS patients experience muscle weakness in their extremities and difficulty with coordination and balance. These symptoms may be severe enough to impair walking or even standing. In the worst cases, MS can produce partial or complete paralysis. MS is not considered a fatal disease, as the vast majority of people with MS live a normal life-span. But the unpredictability of the disease can present many challenges, including the possibility of facing increasing limitations.

Most people experience MS symptoms between the ages of 20 and 40. At least two to three times more women than men have been diagnosed with MS. MS occurs in most ethnic groups, including African-Americans, Asians and Latinos, but is more common in Caucasians of northern European ancestry.

Treatment of MS focuses on symptom management, treatment of attacks, and reduction of disease progression. Of the nine FDA-approved, disease modifying treatments introduced since 1993, three are interferon-based, two are immunomodulators, one is an immunosuppressant, one is an antineoplastic, one is a monoclonal antibody, and one’s exact mechanism is unknown. (Source: National MS Society).

While disease-modifying treatments reduce the progression rate of the disease, they do not stop it. As multiple sclerosis progresses, the symptomatology tends to increase. Therefore, MS treatment management includes symptomatic treatments as well as rehabilitative and psychological approaches such as physical therapy, speech therapy, occupational therapy, support groups, an exercise program, a healthy lifestyle, good nutrition, rest and relaxation.

The variable clinical presentation of MS and the lack of established diagnostic laboratory tests lead to delays and difficulties in diagnosis. New diagnostic methods are being investigated as well as biomarkers for monitoring disease activity.

Parkinson’s Disease (PD)

PD is a chronic, progressive disorder, affecting certain nerve cells, which reside in the Substantia Nigra of the brain and which produce dopamine, a neurotransmitter that directs and controls movement. In PD, these

dopamine-producing nerve cells break down, causing dopamine levels to drop below the threshold levels and resulting in brain signals directing movement to become abnormal. The cause of the disease is unknown.

Over 6.3 million people worldwide suffer from PD, of whom about one million are in the United States. Most people are diagnosed with the disease between the ages of 55 and 65 and about 85% of people with PD are over the age of 65. Prevalence of PD is increasing in line with the general aging of the population. The market for pharmaceutical treatments for PD has been estimated to be $2.4 billion a year in the U.S., France, Germany, Italy, Spain, the United Kingdom and Japan. However, these costs are dwarfed when compared to the total economic burden of the disease, which has been estimated by the National Parkinson Foundation to exceed $14 billion annually in the U.S. alone, including costs of medical treatment, caring, facilities and other services, as well as loss of productivity of both patients and caregivers.

The symptoms of PD include shaking (tremor), stiff muscles (rigidity) and slow movement (Bradykinesia). A person with fully developed PD may also have a stooped posture, a blank stare or fixed facial expression, speech problems and difficulties with balance or walking. Although it can be highly debilitating, the disease is not life threatening and an average patient’s life span is approximately 20 years from the onset of symptoms.

Treatment of PD primarily comprises dopamine replacement, either directly (levodopa), with dopamine mimetics or by inhibition of its breakdown. These treatments focus on treating the symptoms of the disease and are not a cure for PD.

Levodopa, which remains the standard and most potent PD medication available, has a propensity to cause serious motor response complications with long-term use. Moreover, effective drug dosage often requires gradual increase, leading to more adverse side effects and eventual resistance to its therapeutic action. This greatly limits patient benefit. Therefore, physicians and researchers have sought levodopa-sparing strategies in patients with early-stage disease to delay the need for levodopa.

PD is also treated by Deep Brain Stimulation ("DBS"), which consists of implanting electrodes deep into the brain to provide permanent electrical stimulation to specific areas of the brain and to cause a delay in the activity in those areas. However, DBS is problematic as it can cause uncontrollable and severe side effects such as bleeding in the brain, infection and depression. In addition, like drug therapy, DBS focuses on treating the symptoms of PD and does not provide a cure.

There is a greatly unsatisfied need for novel approaches towards management 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 addition to the symptomatic drug development approaches, there is an intense effort to develop cell and gene therapeutic "curative" approaches to restore the neural function in patients with PD, by (i) replacing the dysfunctional cells with dopamine producing cell transplant, or by (ii) providing growth factors and proteins, such as GDNF, that can maintain or preserve the patient's remaining dopaminergic cells, protecting them from further degeneration. Preclinical evaluation of cell therapeutic approaches based on transplantation of dopaminergic neurons differentiated *in-vitro* from ESC, have been successful in ameliorating PD in animal models, as has direct gene therapy with vectors harboring the GDNF gene. However, these approaches are limited, in the first case, by the safety and ethical considerations associated with use of ESC, and, in the second case, by the safety risks inherent to gene therapy. As a result, intensive efforts have been made to develop an adult stem-cell based treatment.

Company Business Strategy

Our company is focused on advancing the NurOwn treatment, with the goal of obtaining FDA regulatory approval for uses as a treatment of ALS patients.

- Phase IIa dose-escalating safety and preliminary efficacy clinical trial in Israel;
- Phase II ALS safety and preliminary efficacy clinical trial in the United States; and
- Phase II/III repeat dose clinical efficacy trial.

Additional strategic goals of the Company:

- Development of a customized NurOwn bioreactor for optimization and scale-up of NurOwn production;
- Development of additional clinical indications, i.e. MS;
- Pursuing strategic partnerships with pharmaceutical companies as we progress towards advanced clinical development and commercialization.

Sales and Marketing

We intend to establish and maintain fully-equipped cGMP-certified Cell-Processing Centers in strategic locations to conduct NurOwn production and distribution over the broadest geographic area. Each Cell-Processing Center would receive an initial Bone Marrow sample of the patient, harvested at a medical center. The patient's MSC cells would be isolated and expanded, in order to produce an initial dose of NurOwn cells. A master cell bank for each individual patient would be maintained for production of subsequent, future NurOwn doses on a long-term basis. These doses

would be produced as needed and transported to the medical centers, where they would then be transplanted back into the patient.

We intend to seek partnering opportunities with a strategic partner as we progress towards advanced clinical development and commercialization.

Intellectual Property

Patents:

On January 8, 2014 we announced that we received a Notice of Intention to Grant from the European Patent Office (EPO) for our patent application entitled "Isolated Cells and Populations Comprising Same for the Treatment of CNS Diseases" (European serial number EP 06766101.7) . This patent relates to the production method for the company's proprietary stem cells induced to secrete large quantities of neurotrophic factors for the treatment of neurodegenerative diseases.

On February 11, 2014 we were granted a U.S. Patent (No. 8,647,874) for the same patent application as above.

On March 4, 2014 we were granted a U.S. Patent (No. 8,663,987) for our “Mesenchymal Stem Cells for the Treatment of CNS Diseases” (serial number 12/994,761) patent application. This patent relates to our proprietary stem cells induced to secrete large quantities of neurotrophic factors for the treatment of neurodegenerative diseases.

We have pending patent applications in (1) the United States; (2) Europe; (3) Israel; and (4) Hong Kong, as follows:

A. The Israeli Subsidiary is the sole owner of United States Provisional patent application Serial No. 61/679,822, filed August 6, 2012, entitled "Methods of Generating Mesenchymal Stem Cells Which Secrete Neurotrophic Factors.” This application has now been filed as International Application No.: PCT IL2013/050660.

This invention is directed to a method of generating MSCs which secrete neurotrophic factors (“NTFs”) comprising incubating a population of undifferentiated MSCs in a differentiating medium comprising basic fibroblast growth factor (“bFGF”), platelet derived growth factor (“PDGF”), heregulin and cAMP. The application also covers a method of treating a disease for which administration of neurotrophic factors is beneficial in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of isolated population of MSCs which secretes neurotrophic factors made according to the above method. Also taught is a method of selecting MSCs which secrete NTFs from a mixed population of MSCs, comprising (a) analyzing the cells of said mixed population of cells for at least one of the following parameters: (i) cells which express CD44 below a predetermined threshold, or (ii) cells which express CD73 above a predetermined threshold; and (b) selecting cells which are positive for at least one of said parameters, thereby selecting the MSCs which secrete neurotrophic factors. The application teaches a pharmaceutical composition comprising the isolated population of MSCs as an active agent and a pharmaceutically acceptable carrier.

B. The Israeli Subsidiary is co-owner, with Ramot, in the invention entitled “Mesenchymal Stem Cells for the Treatment of CNS Diseases”, filed as a PCT application on May 26, 2009, currently pending as National Phase patent applications in the following countries:

- United States: Serial No. 12/994,761
- United States: Serial No. 14/164,286
- Europe: Serial No. 09754337.5
- Europe: Serial No. 13164650.7
- Israel: Serial No. 209604
- Hong Kong: Serial No. 11107062.5
- Hong Kong: Serial No. 13109415.3

This invention is directed to an isolated human cell comprising at least one mesenchymal stem cell phenotype and secreting brain-derived neurotrophic factor (“BDNF”), wherein a basal secretion of the BDNF is at least five times greater than a basal secretion of the BDNF in a mesenchymal stem cell. Also disclosed in this application is an isolated cell population comprising human mesenchymal stem cells, wherein at least 50% of the cells express glial fibrillary acidic protein (“GFAP”) and secrete at least one neurotrophic factor. Also taught is an isolated cell population comprising human cells wherein (i) at least N% of said human cells secreting BDNF, wherein a basal secretion of said BDNF is at least five times greater than a basal secretion of the BDNF in a mesenchymal stem cell; (ii) at least M% of said human cells comprise at least one mesenchymal stem cell phenotype; and (iii) at least one of the human cells secretes the BDNF and the mesenchymal stem cell phenotype; where M and N are each independently selected between 1 and 99. Methods of generating same and uses of same are also disclosed. The method of generating cells useful for treating a CNS disease or disorder comprises (a) incubating mesenchymal stem cells in a culture medium comprising platelet lysate to generate propagated mesenchymal stem cells; and (b) incubating said propagated mesenchymal stem cells in a differentiating medium, thereby generating cells useful for treating the CNS disease or disorder. Another method taught is that of generating cells secreting neurotrophic factors, comprising (i) incubating mesenchymal stem cells in a serum free medium comprising platelet lysate to generate propagated mesenchymal stem

cells; and (ii) incubating the propagated mesenchymal stem cells in a differentiating medium comprising at least one differentiating agent, said at least one differentiating agent being selected from the group consisting of platelet derived growth factor ("PDGF"), human neuregulin 1-b1, FGF2, EGF, N2, IBMX and cAMP, thereby generating cells secreting neurotrophic factors. The European applications claim an isolated human cell comprising a cell being non-genetically manipulated, and characterized by: a) expressing tyrosine hydroxylase, nestin and H-NF and b) secreting BDNF, and c) not secreting nerve growth factor ("NGF") wherein a basal secretion of said BDNF is at least five times greater than a basal secretion of said BDNF in a mesenchymal stem cell; an isolated cell population comprising cells generated from human bone marrow derived cells expressing CD73, CD90 and CD105 and not expressing CD14, CD19, CD34, CD45 and HLA-DR, wherein at least 50% of the cells of the cell population express GFAP and secrete BDNF; and a method of generating cells useful for treating a CNS disease or disorder, the method comprising: (1) incubating bone marrow derived cells expressing CD73, CD90 and CD105 and not expressing CD14, CD19, CD34, CD45 and HLA-DR in a culture medium comprising human platelet lysate to generate propagated cells; and (2) incubating said propagated cells in a medium comprising a differentiating agent, thereby generating cells useful for treating the CNS disease or disorder, wherein said differentiating agent is selected from the group consisting of PDGF, human neuregulin 1- 1, FGF2, EGF, N2, IBMX and cAMP.

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C. The Israeli Subsidiary is the licensee of the following patent applications owned by Ramot under terms set forth in the Second Ramot Agreement and the Assignment Agreement, as follows:

1. Invention entitled "Isolated Cells and Populations Comprising Same for the Treatment of CNS Diseases", filed as a PCT application on June 18, 2006, currently pending as National Phase patent applications in the following countries:

- Europe: Serial No. 06766101.7
- Europe: Serial No. 11000994.1
- Hong Kong: Serial No. 12112468.4
- United States: Serial No. 11/727,583, Continuation-in-Part filed on March 27, 2007
- United States: Serial No. 14/173,846

This invention is directed to an isolated human cell and populations thereof comprising at least one astrocytic phenotype and at least one mesenchymal stem cell phenotype, wherein the mesenchymal stem cell phenotype is not an astrocytic phenotype; an isolated human cell comprising at least one mesenchymal stem cell phenotype and at least one astrocytic structural phenotype, wherein the mesenchymal stem cell phenotype is not an astrocytic structural phenotype; or an isolated human cell comprising at least one mesenchymal stem cell phenotype and at least one astrocytic functional phenotype, wherein the mesenchymal stem cell phenotype is not an astrocytic functional phenotype. Also taught is a method of generating astrocyte-like cells expressing S100 beta, glial fibrillary acidic protein (GFAP), glutamine sythetase, GLAST, GLTI and glial derived neurotrophic factor (GDNF) comprising (a) culturing mesenchymal stem cells in a medium comprising human epidermal growth factor (hEGF) and human basic fibroblast growth factor (hbFGF); and (b) incubating the mesenchymal stem cells in a differentiating medium comprising platelet derived growth factor (PDGF) and human neuregulin 1-b1, thereby generating astrocyte-like cells. Another disclosed method of generating astrocyte-like cellse teaches (i) incubating mesenchymal stem cells in a medium comprising hEGF and hbFGF to generate cells predisposed to generate into astrocyte-like cells; and (ii) incubating the predisposed cells in a differentiating medium comprising PDGF and human neuregulin 1-b1, thereby generating astrocyte-like cells.

2. Invention entitled "Methods, nucleic acid constructs and cells for treating neurodegenerative disorders", filed on May 17, 2005 as United States patent application Serial No. 13/783,607. This invention is directed to a method of treating a neurodegenerative disorder by administering to an individual in need thereof cells capable of exogenously regulatable neurotransmitter synthesis. The cells are produced by incubating bone marrow stromal cells in a differentiating medium comprising docosahexaenoic acid or arachidonic acid and at least one differentiating agent.

Trademarks:

We own a pending United States application to register the trademark NUROWN (application no. 85154891, filed October 18, 2010) for use in connection with "compositions of cells derived from stem cells for medical purposes; stem cells for medical purposes." The application was filed based on an intent-to-use the mark, but has not matured to registration yet.

The patent applications, as well as relevant know-how and research results are licensed from Ramot. We intend to work with Ramot to protect and enhance our mutual intellectual property rights by filing continuations and divisional patent applications. New discoveries arising in the course of research and development within the Company will be patented by us independently.

Research and License Agreement with Ramot

On July 12, 2004, we entered into a Research and License Agreement (the "Original Ramot Agreement") with Ramot, the technology licensing company of Tel Aviv University, which agreement was amended on March 30, 2006 by the

Amended Research and License Agreement (described below). Under the terms of the Original Ramot Agreement, Ramot granted to us a license to (i) the inventions, know-how and results made with respect to the above-mentioned stem cell technology developed by the team led by Prof. Melamed and Prof. Offen in the course of performance of the research, and the patents and pending patent applications owned by Ramot, and (ii) the results of further research to be performed by the same team on the development of the stem cell technology. Simultaneously with the execution of the Original Ramot Agreement, we entered into individual consulting agreements with Prof. Melamed and Prof. Offen pursuant to which all intellectual property developed by Prof. Melamed or Prof. Offen in the performance of services thereunder will be owned by Ramot and licensed to us under the Original Ramot Agreement.

On March 30, 2006 and May 23, 2006, we entered into an Amended Research and License Agreement and an Amendment Agreement to the Amended Research and License Agreement, respectively (the "Amended Research and License Agreement") with Ramot. Under the Amended Research and License Agreement, the funding of further research relating to the licensed technology in an amount of $570,000 per year was reduced to $380,000 per year. Moreover, under the Amended Research and License Agreement, the initial period of time that we agreed to fund the research was extended from an initial period of two (2) years to an initial period of three (3) years. The Amended Research and License Agreement also extended the additional two-year period in the Original Ramot Agreement to an additional three-year period, if certain research milestones were met.

We entered into a Second Amended and Restated Research and License Agreement with Ramot on July 26, 2007, effective July 12, 2004 (the "Second Ramot Agreement"), which amended and replaced the Amended Research and License Agreement. The Second Ramot Agreement imposed on us development and commercialization obligations, milestone and other obligations. The license was granted in consideration for (i) royalty payments ranging from three percent (3%) to five percent (5%) of all net sales and (ii) potential payments concerning sublicenses ranging from twenty percent (20%) to twenty-five percent (25%) of sublicense receipts. In addition, in the event that the research period was extended for an additional three year period in accordance with the terms of the Second Ramot Agreement, then we had to make payments to Ramot for each year of the extended research period in the amount of $380,000. As of June 30, 2007, we owed Ramot an aggregate amount of $513,249 in overdue payments and patent fees under the Amended Research and License Agreement.

On August 1, 2007, we obtained a waiver and release from Ramot pursuant to which Ramot agreed to an amended payment schedule regarding our payment obligations under the Second Ramot Agreement and waived all claims against us resulting from our previous breaches, defaults and non-payment under the Amended Research and License Agreement.

After our failure to meet the amended payment schedule and subsequent negotiations, on December 24, 2009, we entered into a Letter Agreement and an amended agreement to the Second Ramot Agreement (collectively, the "Letter Agreement") with Ramot, pursuant to which, among other things, Ramot agreed to: (i) release us from our obligation to fund three years of additional research (which would have totaled $1,140,000) and (ii) accept conversion of certain research payments due in the amount of $272,000 into 1,120,000 shares of our common stock. Pursuant to the Letter Agreement, we agreed, among other things, to: (i) reimburse Ramot for outstanding patent-related expenses; and (ii) abandon our rights in certain joint patent rights and patents of Ramot in certain countries.

As of February 2011, Ramot had sold the 1,120,000 shares of common stock of the Company for approximately $235,000 and we paid the remaining $5,000 due to Ramot. To date there is no additional debt to Ramot.

On December 20, 2011, we entered into an Assignment Agreement with our Israeli Subsidiary (the "Assignment Agreement"), with the consent of Ramot. Under the Assignment Agreement, we assigned and transferred all of our rights, interests, titles, liabilities and obligations (the "Rights") under the Second Ramot Agreement to our Israeli Subsidiary, effective as of January 1, 2007 and our Israeli Subsidiary agreed to assume all such Rights. We agreed to be a guarantor of all obligations of our Israeli Subsidiary under the Second Ramot Agreement and Ramot can look to us to demand compliance with the Second Ramot Agreement.

In May 2012, we, the Israeli Subsidiary and Prof. Offen entered into a Consulting Agreement, effective as of January 1, 2012, which replaced the previous consulting agreement, dated July 31, 2004, pursuant to which all work product resulting from the provision of services will vest solely with the Israeli Subsidiary and if any work product resulting from the provision of services results in the creation or development of intellectual property it will be deemed a joint invention, and will be jointly owned by Ramot and the Israeli Subsidiary.

Government Regulations and Supervision

Government Regulation and Product Approval

Once fully developed, we intend to market our bone marrow derived differentiated neurothrophic-factor secreting cell products, NurOwn, for autologous transplantation in patients by neurosurgeons in medical facilities in the U.S., Europe, Japan and the Pacific Rim. We plan to submit biologics license application ("BLA") in the United States from the development of NurOwn for the treatment of ALS patients. We initiated the regulatory process with a Pre-IND meeting with the FDA in September 2012, and submtted our IND application in December 2013. We have retained expert regulatory consultants to assist us in our approaches to the FDA.

In January 2013, the EMA Committee for Advanced Therapies classified NurOwn as an Advanced Therapy Medicinal Product.

Government authorities in the United States at the federal, state and local level extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, marketing, export and import of products such as those we are developing. Our product candidates must receive final approval from the FDA before they may legally be marketed in the United States or by the appropriate foreign regulatory agency before it may be legally marketed in foreign countries.

U.S. Drug Development Process

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and implementing regulations. Drugs are also subject to other federal, state and local statutes and regulations. Biologics are subject to regulation by the FDA under the FDCA, the Public Health Service Act, or the PHSA, and related regulations and other federal, state and local laws and regulations. Biological products are therapies used to treat disease and health conditions. They include a wide variety of products including vaccines, blood and blood components, gene therapies, tissue and proteins. Unlike most prescription products made through chemical processes, biological products generally are made from human and/or animal materials. To be lawfully marketed in interstate commerce, a biologic product must be the subject of a BLA, issued by the FDA on the basis of a demonstration that the product is safe, pure and potent, and that the facility in which the product is manufactured meets standards to assure that it continues to be safe, pure and potent. The FDA has developed and is continuously updating the requirements with respect to cell and gene therapy products and has issued documents concerning the regulation of cellular and tissue-based products. Manufacturers of cell and tissue-based products must comply with the FDA’s current good tissue practices, or cGTP, which are FDA regulations that govern the methods used in, and the facilities and controls used for, the manufacture of such products. The primary intent of the cGTP requirements is to ensure that cell and tissue based products are manufactured in a manner designed to prevent the introduction, transmission and spread of communicable disease.

The process of obtaining regulatory approvals and ensuring compliance with appropriate federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process, or after approval, may subject an applicant to administrative or judicial sanctions. These sanctions could include the FDA's refusal to approve pending applications, withdrawal of an approval, a clinical hold, warning letters, product recalls, product seizures, product detention, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement or civil or criminal penalties. The process required by the FDA before a biological product or drug may be marketed in the United States generally involves the following:

- Completion of preclinical laboratory tests, animal studies and formulation studies according to Good Laboratory Practices or other regulations;
- Submission to the FDA of an investigational new drug application, or IND, which must become effective before human clinical trials may begin;
- Performance of adequate and well-controlled clinical trials according to Good Clinical Practices, or GCP, to establish the safety and efficacy of the proposed biological product or drug for its intended use;
- submission to the FDA of a new drug application, or NDA, for a new drug; or a biologic license application for a new biological product;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the drug is produced to assess compliance with Good Manufacturing Practices, or cGMP, to assure that the facilities, methods and controls are adequate to preserve the drug's or biologic's identity, strength, quality and purity; and
- FDA review and approval of the BLA or NDA.

The testing and approval process require substantial time, effort and financial resources and we cannot be certain that any approvals for our product candidates will be granted on a timely basis, if at all.

Once a pharmaceutical product candidate is identified for development, it enters the preclinical testing phase. Preclinical tests include laboratory evaluations of product chemistry, toxicity, formulation and stability, as well as animal studies. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data and any available clinical data or literature, to the FDA as part of the IND. The sponsor must also include a protocol detailing, among other things, the objectives of the initial clinical trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated if the initial clinical trial lends itself to an efficacy evaluation. Some preclinical testing may continue even after the IND is submitted. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA places the clinical trial on a clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. Clinical holds also may be imposed by the FDA at any time before or during trials due to safety concerns or non-compliance. Accordingly, we cannot assure you that submission of an IND will result in the FDA allowing clinical trials to begin or, once begun, issues will not arise that result in the suspension or termination of such trial.

All clinical trials must be conducted under the supervision of one or more qualified investigators in accordance with GCP regulations. These regulations include the requirement that all research subjects provide informed consent. Further, an institutional review board, or IRB, must review and approve the plan for any clinical trial before it commences at any institution. An IRB considers, among other things, whether the risks to individuals participating in the trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the information regarding the clinical trial and the consent form that must be provided to each clinical trial subject or his or her legal representative and must monitor the clinical trial until completed. Once an IND is in effect, each new clinical protocol and any amendments to the protocol must be submitted to the IND for FDA review, and to the IRBs for approval.

Human clinical trials are typically conducted in three sequential phases that may overlap or be combined:

- *Phase 1.* The product is initially introduced into healthy human subjects and tested for safety, dosage tolerance, absorption, metabolism, distribution and excretion. In the case of some products for severe or life-threatening diseases, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing may be conducted in patients having the specific disease.
- *Phase 2.* Phase 2 trials involve investigations in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and the optimal dosage and schedule.
- *Phase 3.* Clinical trials are undertaken to further evaluate dosage, clinical efficacy and safety in an expanded patient population at geographically dispersed clinical trial sites. These trials are intended to establish the overall risk/benefit ratio of the product and provide an adequate basis for regulatory approval and product labeling.

Post-approval studies, also called Phase 4 trials, may be conducted after initial marketing approvals. These studies are used to obtain additional experience from the treatment of patients in the intended therapeutic indication and may be required by the FDA as part of the approval process.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and safety reports must be submitted to the FDA and the investigators for serious and unexpected side effects. Phase 1, Phase 2 and Phase 3 testing may not be completed successfully within any specified period, if at all. The FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug or biologic has been associated with unexpected serious harm to patients.

Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the product and finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the manufacturer must develop methods for testing the identity, strength, quality and purity of the final product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

During the development of a new drug or biologic, a sponsor may be able to request a Special Protocol Assessment, or SPA, the purpose of which is to reach agreement with the FDA on the Phase 3 clinical trial protocol design and analysis that will form the primary basis of an efficacy claim. An SPA is intended to provide assurance that if the agreed upon clinical trial protocol is followed, the clinical trial endpoints are achieved, and there is a favorable risk-benefit profile, the data may serve as the primary basis for an efficacy claim in support of a BLA or an NDA. However, an SPA is not a guarantee of an approval of a product candidate or any permissible claims about the product candidate. In particular, SPAs are not binding on the FDA if previously unrecognized public health concerns arise during the performance of the clinical trial, other new scientific concerns regarding product candidate's safety or efficacy arise, or if the sponsoring company fails to comply with the agreed upon clinical trial protocol.

The results of product development, preclinical studies and clinical trials, along with descriptions of the manufacturing process, analytical tests conducted on the biologic or drug, proposed labeling and other relevant information, are submitted to the FDA as part of an NDA or BLA, requesting approval to market the product. The submission of an NDA or BLA is subject to the payment of substantial user fees which may be waived under certain limited circumstances.

FDA Review of Biologics License Applications and New Drug Applications

The FDA reviews all BLAs and NDAs submitted to ensure that they are sufficiently complete for substantive review before it accepts them for filing. The FDA may request additional information rather than accept a BLA or an NDA for filing. In this event, the BLA or NDA must be re-submitted with the additional information. The re-submitted application also is subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. Under the goals and policies agreed to by the FDA under the Prescription Drug User Fee Act, or PDUFA, the FDA has ten months in which to complete the initial review of a standard BLA or NDA and respond to the applicant and six months for a priority BLA or NDA. The FDA does not always meet its PDUFA goal dates for standard and priority BLAs or NDAs. The FDA reviews an NDA to determine, among other things, whether a product is safe and effective for its intended use and whether its manufacturing is cGMP-compliant to assure and preserve the product's identity, strength, quality and purity. The FDA reviews a BLA to determine, among other things, whether the product is safe, pure, and potent and the facility in which it is manufactured, processed, packaged or held meets standards designed to assure the products continued safety, purity

and potency. Before approving an NDA or BLA, the FDA will inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements, and additionally, in the case of biologics in accordance with cGTP guidelines, and adequate to assure consistent production of the product within required specifications. The FDA may refer the NDA or BLA to an advisory committee for review, evaluation and recommendation as to whether the application should be approved and under what conditions. An advisory committee is a panel of independent experts who provide advice and recommendations when requested by the FDA on matters of importance that come before the agency. The FDA is not bound by the recommendation of an advisory committee.

The approval process is lengthy and difficult and the FDA may refuse to approve a BLA an NDA if the applicable regulatory criteria are not satisfied or may require additional clinical data or other data and information.

Even if such data and information is submitted, the FDA may ultimately decide that the BLA or NDA does not satisfy the criteria for approval. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret the same data. The FDA will issue a complete response letter if the agency decides not to approve the BLA or NDA in its present form. The complete response letter usually describes all of the specific deficiencies that the FDA identified in the BLA or NDA. The deficiencies identified may be minor, for example, requiring labeling changes, or major, for example, requiring additional clinical trials. Additionally, the complete response letter may include recommended actions that the applicant might take to conform the application to a condition suitable for approval. If a complete response letter is issued, the applicant may either resubmit the BLA or NDA, addressing all of the deficiencies identified in the letter, withdraw the application, or request an opportunity for a hearing.

If a product receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling. In addition, the FDA may require Phase 4 testing which involves clinical trials designed to further assess a drug's or biologic's safety and effectiveness after BLA or NDA approval and may require testing and surveillance programs to monitor the safety of approved products that have been commercialized.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biological product intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making a drug or biological product available in the United States for this type of disease or condition will be recovered from sales of the product. Orphan product designation must be requested before submitting an NDA or BLA. After the FDA grants orphan product designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process. In addition to the potential for a period of exclusivity, we may be eligible for grant funding of up to $400,000 per year for four years to defray costs of clinical trial expenses, tax credits for clinical research expenses and potential exemption from the FDA application user fee.

If a product that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same drug or biological product for the same indication for seven years, except in limited circumstances, such as (i) the drug's orphan designation is revoked; (ii) its marketing approval is withdrawn; (iii) the orphan exclusivity holder consents to the approval of another applicant's product; (iv) the orphan exclusivity holder is unable to assure the availability of a sufficient quantity of drug; or (v) a showing of clinical superiority to the product with orphan exclusivity by a competitor product. Competitors, however, may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity. Orphan product exclusivity also could block the approval of one of our products for seven years if a competitor obtains approval of the same drug or biological product as defined by the FDA or if our drug or biological candidate is determined to be contained within the competitor's product for the same indication or disease. If a drug or biological product designated as an orphan product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan product exclusivity. Orphan drug status in the European Union has similar but not identical benefits in the European Union.

In February 2011, we received Orphan Drug Designation for NurOwn for the treatment of ALS in the United States. In July 2013, we received Orphan Medicinal Product Designation for NurOwn for the treatment of ALS from the European Commission.

Patent Term Restoration and Marketing Exclusivity

Depending upon the timing, duration and specifics of FDA marketing approval of our product candidates, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between (a) the effective date of an IND and the submission date of a BLA or an NDA

plus (b) the time between the submission date of a BLA or an NDA and the approval of that application. Only one patent applicable to an approved drug or biologic is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent and within 60 days of approval of the drug or biologic. The U.S. patent and Trademark Office, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration.

Biologics Price Competition and Innovation Act of 2009

The Biologics Price Competition and Innovation Act of 2009, or BPCIA, amended the PHSA to create a new licensure framework for biosimilar products, which could ultimately subject our biological product candidates to competition. Under the BPCIA, a manufacturer may submit an application for licensure of a biological product that is "biosimilar to" or "interchangeable with" a referenced, branded biologic product. Previously, there had been no licensure pathway for such biosimilar or interchangeable products. For purposes of the BPCIA, a reference product is defined as the single biological product licensed under a full BLA against which a biological product is evaluated in an application submitted under a follow-on BLA.

The BPCIA also created a 12-year period of reference product exclusivity, which can be extended to 12.5 years with pediatric exclusivity. The 12-year exclusivity period begins on the date of first licensure of the reference product under the PHSA and during which the licensure of a follow-on application for a biosimilar or interchangeable product cannot be made effective. During the first four years (or four and one-half years with pediatric exclusivity) of the 12-year period, an application for a biosimilar or interchangeable version of the reference product cannot be submitted to the FDA. Under budget proposals submitted by President Obama, the Administration has requested that reference product exclusivity would decrease from twelve to seven years. Congress has not yet enacted such a change in the BPCIA, but could move to enact such a decrease in the reference product exclusivity period.

The BPCIA includes limits on obtaining 12-year reference product exclusivity for certain changes or modifications to the reference product. A separate 12-year reference product exclusivity period does not apply to:

- a BLA supplement for the product that is the reference product;
- a subsequent BLA filed by the same reference product sponsor or manufacturer (or a licensor, predecessor in interest, or other related entity) for a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device or strength; or
- a modification to the structure of the biological product that does not result in a change in safety, purity or potency.

In February 2012, the FDA issued three draft guidance documents on biosimilar product development. The FDA is soliciting comments on the draft guidance documents which are described by the FDA as follows: (1) Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, which is intended to assist companies in demonstrating that a proposed therapeutic protein product is biosimilar to a reference product for the purpose of submitting an application, called a "351(k)" application, to the FDA. This draft guidance describes a risk-based "totality-of-the-evidence" approach that the FDA intends to use to evaluate the data and information submitted in support of a determination of biosimilarity of the proposed product to the reference product; (2) Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product, which provides an overview of analytical factors to consider when assessing biosimilarity between a proposed therapeutic protein product and a reference product for the purpose of submitting a 351(k) application; and (3) Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, which provides answers to common questions from people interested in developing biosimilar products. We cannot predict when or whether these draft guidance documents will ever be finalized or what changes the agency may make in its approach to implementation of the BPCIA.

In addition to creating a 12-year period of reference product exclusivity, the BPCIA clarifies the interaction of that exclusivity with orphan drug exclusivity, such that, if a reference product has been designated for a rare disease or condition the licensure of a biosimilar or interchangeable version of a reference product for such disease or condition may only occur after the later of the expiration of any applicable seven-year orphan drug exclusivity or the 12-year reference product exclusivity (or seven and one-half years and 12.5 years with pediatric exclusivity).

Our biological product candidates, if approved, could be considered reference products entitled to 12-year exclusivity. Even if our products are considered to be reference products eligible for exclusivity, another company could market a competing version of any of our biological products if the FDA approves a full BLA for such product containing the sponsor's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of their product.

The BPCIA also sets forth a complex mechanism for resolving patent disputes that involves a step-wise exchange of information prior to the initiation of a patent infringement lawsuit against a biosimilar or interchangeable product sponsor. Unlike the Hatch-Waxman Act, the BPCIA provides no automatic stay on approval of a biosimilar product application, except an interchangeable product receives the lesser of one year of exclusivity after the date of first commercial marketing or 18 months of exclusivity after a final court decision or dismissal of a patent challenge or, if the applicant has not been sued, after approval. The BPCIA does not prevent a competitor from conducting its own clinical trials and submitting a full BLA on the same or similar product.

Post-Approval Requirements

Any drugs for which we receive FDA approval are subject to continuing regulation by the FDA, including, among other things, record-keeping requirements, reporting of adverse effects with the product, reporting of changes in distributed products which would require field alert reports (FARs) for drugs and biological product deviation reports

(BPDRs), providing the FDA with updated safety and efficacy information, product sampling and distribution requirements, complying with certain electronic records and signature requirements and complying with FDA promotion and advertising requirements. In September 2007, the Food and Drug Administration Amendments Act of 2007 was enacted, giving the FDA enhanced post-marketing authority, including the authority to require postmarketing studies and clinical trials, labeling changes based on new safety information, and compliance with risk evaluations and mitigation strategies, or REMS, approved by the FDA. The FDA strictly regulates labeling, advertising, promotion and other types of information on products that are placed on the market. Drugs and biologics may be promoted only for the approved indications and in accordance with the provisions of the approved label. Further, manufacturers of drugs and biologics must continue to comply with cGMP requirements, which are extensive and require considerable time, resources and ongoing investment to ensure compliance. In addition, changes to the manufacturing process generally require prior FDA approval before being implemented and other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval.

Drug and biologic manufacturers and other entities involved in the manufacturing and distribution of approved drugs and biologics are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP, GTP applicable to biologics, and other laws. The cGMP requirements apply to all stages of the manufacturing process, including the production, processing, sterilization, packaging, labeling, storage and shipment of the drug. Manufacturers must establish validated systems to ensure that products meet specifications and regulatory standards, and test each product batch or lot prior to its release.

The FDA may withdraw a product approval if compliance with regulatory standards is not maintained or if problems occur after the product reaches the market. Discovery of previously unknown problems with a product subsequent to its approval may result in restrictions on the product or even complete withdrawal of the product from the market. Further, the failure to maintain compliance with regulatory requirements may result in administrative or judicial actions, such as fines, warning letters, holds on clinical trials, product recalls or seizures, product detention or refusal to permit the import or export of products, refusal to approve pending applications or supplements, restrictions on marketing or manufacturing, injunctions or civil or criminal penalties.

From time to time, legislation is drafted, introduced and passed in Congress that could significantly change the statutory provisions governing the approval, manufacturing and marketing of products regulated by the FDA. In addition to new legislation, the FDA regulations and policies are often revised or reinterpreted by the agency in ways that may significantly affect our business and our product candidates. It is impossible to predict whether further legislative or FDA regulation or policy changes will be enacted or implemented and what the impact of such changes, if any, may be.

Foreign Regulation

In addition to regulations in the United States, we will be subject to a variety of foreign regulations governing clinical trials and commercial sales and distribution of our product candidates to the extent we choose to clinically evaluate or sell any products outside of the United States. Whether or not we obtain FDA approval for a product, we must obtain approval of a product by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of the product in those countries. The approval process varies from country to country and the time may be longer or shorter than that required for FDA approval. The requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary greatly from country to country. As in the United States, post-approval regulatory requirements, such as those regarding product manufacture, marketing, or distribution would apply to any product that is approved outside the United States.

Third Party Payor Coverage and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any of our biologic or drug candidates for which we obtain regulatory approval. In both the United States and foreign markets, our ability to commercialize our product candidates successfully, and to attract commercialization partners for our product candidates, depends in significant part on the availability of adequate financial coverage and reimbursement from third party payors, including, in the United States, governmental payors such as the Medicare and Medicaid programs, managed care organizations, and private health insurers. Medicare is a federally funded program managed by the Centers for Medicare and Medicaid Services, or CMS, through local fiscal intermediaries and carriers that administer coverage and reimbursement for certain healthcare items and services furnished to the elderly and disabled. Medicaid is an insurance program for certain categories of patients whose income and assets fall below state defined levels and who are otherwise uninsured that is both federally and state funded and managed by each state. The federal government sets general guidelines for Medicaid and each state creates specific regulations that govern its individual program. Each payor has its own process and standards for determining whether it will cover and reimburse a procedure or particular product. Private payors often rely on the lead of the governmental payors in rendering coverage and reimbursement determinations. Therefore, achieving favorable CMS coverage and reimbursement is usually a significant gating issue for successful introduction of a new product. The competitive position of some of our products will depend, in part, upon the extent of coverage and adequate reimbursement for such products and for the procedures in which such products are used. Prices at which we or our customers seek reimbursement for our product candidates can be subject to challenge, reduction or denial by the government and other payors.

The U.S. Congress and state legislatures may, from time to time, propose and adopt initiatives aimed at cost containment, which could impact our ability to sell our product candidates profitably. For example, in March 2010,

President Obama signed into law the Patient Protection and Affordable Care Act and the associated reconciliation bill, which we refer to collectively as the Health Care Reform Law, a sweeping law intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. Effective October 1, 2010, the Health Care Reform Law revises the definition of “average manufacturer price” for reporting purposes, which could increase the amount of Medicaid drug rebates to states once the provision is effective. Further, the law imposes a significant annual fee on companies that manufacture or import branded prescription drug products. Substantial new provisions affecting compliance have also been enacted, which may require us to modify our business practices with healthcare practitioners. We will not know the full effects of the Health Care Reform Law until applicable federal and state agencies issue regulations or guidance under the new law.

Although it is too early to determine the effect of the Health Care Reform Law, the new law appears likely to continue the pressure on pharmaceutical pricing, especially under the Medicare program, and may also increase our regulatory burdens and operating costs. Moreover, in the coming years, additional changes could be made to governmental healthcare programs that could significantly impact the success of our product candidates.

The cost of pharmaceuticals continues to generate substantial governmental and third party payor interest. We expect that the pharmaceutical industry will experience pricing pressures due to the trend toward managed healthcare, the increasing influence of managed care organizations and additional legislative proposals. Our results of operations could be adversely affected by current and future healthcare reforms.

Some third party payors also require pre-approval of coverage for new or innovative devices, biologics or drug therapies before they will reimburse healthcare providers that use such therapies. While we cannot predict whether any proposed cost-containment measures will be adopted or otherwise implemented in the future, the announcement or adoption of these proposals could have a material adverse effect on our ability to obtain adequate prices for our product candidates and operate profitably.

Different pricing and reimbursement schemes exist in other countries. In the European Community, governments influence the price of pharmaceutical products through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular drug or biological candidate to currently available therapies. Other member states allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription drugs and biologics, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert a commercial pressure on pricing within a country.

Other Healthcare Laws and Compliance Requirements

In the United States, our activities are potentially subject to regulation by various federal, state and local authorities in addition to the FDA, including the Centers for Medicare and Medicaid Services, other divisions of the United States Department of Health and Human Services (e.g., the Office of Inspector General), the United States Department of Justice and individual United States Attorney offices within the Department of Justice, and state and local governments. These regulations include:

- the federal healthcare program anti-kickback law, which prohibits, among other things, persons from soliciting, receiving or providing remuneration, directly or indirectly, to induce either the referral of an individual, for an item or service or the purchasing or ordering of a good or service, for which payment may be made under federal healthcare programs such as the Medicare and Medicaid programs;
- federal false claims laws which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other government reimbursement programs that are false or fraudulent;
- the federal Health Insurance Portability and Accountability Act of 1996, which prohibits executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters and which also imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information;
- the federal transparency requirements under the Health Care Reform Law requires manufacturers of drugs, devices, biologics, and medical supplies to report to the Department of Health and Human Services information related to physician payments and other transfers of value and physician ownership and investment interests;
- the FDCA, which among other things, strictly regulates drug and biologic product marketing, prohibits manufacturers from marketing drug or biologic products for off-label use and regulates the distribution of drug samples; and
- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third party payor, including commercial insurers, and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by federal laws, thus complicating compliance efforts.

Compliance with Environmental, Health and Safety Laws

In addition to FDA regulations, we are also subject to evolving federal, state and local environmental, health and safety laws and regulations. In the past, compliance with environmental, health and safety laws and regulations has not had a material effect on our capital expenditures. We believe that we comply in all material respects with existing environmental, health and safety laws and regulations applicable to us. Compliance with environmental, health and safety laws and regulations in the future may require additional capital expenditures.

Competition

There are a number of clinical trials underway for potential treatments for ALS, of which only two are stem cell-based trials being conducted by other commercial entities. One is US-based Neuralstem (CUR), which is currently conducting a Phase II trial for its allogeneic, human (fetal) spinal cord derived neural stem cells. The other is Corestem, a Korean company, which is currently conducting two Phase I stem cell-based clinical trials. One is a recently launched Phase I trial with allogeneic bone marrow derived mesenchymal stem cells, and a previous trial, which is not actively recruiting, is with autologous, bone marrow-derived mesenchymal stem cells. There is little public information available about Corestem. Five non-stem cell-based companies are undergoing Phase I/II, Phase II or Phase III clinical trials for ALS. A number of academic institutions are also developing treatment candidates for ALS.

Employees

We currently have 16 employees, 14 of whom are full-time. None of our employees is represented by a labor union.

WHERE YOU CAN FIND MORE INFORMATION

We maintain a website at *www.brainstorm-cell.com*. We make available through our website, free of charge, our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), as soon as reasonably practicable after we electronically file those reports with, or furnish them to, the Securities and Exchange Commission. We also similarly make available, free of charge through our website, the reports filed with the SEC by our executive officers, directors and 10% stockholders pursuant to Section 16 under the Exchange Act. We are not including the information contained at *www.brainstorm-cell.com* or at any other Internet address as part of, or incorporating it by reference into, this Annual Report on Form 10-K.

Item 1A. RISK FACTORS

We operate in a rapidly changing environment that involves a number of risks, some of which are beyond our control. Forward looking statements in this report and those made from time to time by us through our senior management are made under the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Forward looking statements concerning the expected future revenues, earnings or financial results or concerning project plans, performance, or development of products and services, as well as other estimates related to future operations are necessarily only estimates of future results and there can be no assurance that actual results will not materially differ from expectations. Forward-looking statements represent management's current expectations and are inherently uncertain. We do not undertake any obligation to update forward-looking statements. If any of the following risks actually occurs, our financial condition and operating results could be materially adversely affected.

Risks related to our business

We need to raise additional capital. If we are unable to raise additional capital on favorable terms and in a timely manner, we will not be able to execute our business plan and we could be forced to restrict or cease our operations.

We will need to raise additional funds to meet our anticipated expenses so that we can execute our business plan. We expect to incur substantial and increasing net losses for the foreseeable future as we increase our spending to execute our development programs. Our auditors have expressed in their audit report that there is substantial doubt regarding our ability to continue as a going concern.

The amount of financing required will depend on many factors including our financial requirements to fund our research and clinical trials, and our ability to secure partnerships and achieve partnership milestones as well as to fund other working capital requirements. Our ability to access the capital markets or to enlist partners is mainly dependent on the progress of our research and development and regulatory approval of our products.

We expect that the net proceeds of the August 16, 2013 Offering will be insufficient to meet our obligations in the upcoming 12 months, as we commence and pursue clinical trials in the United States, and that additional capital will be required in order to finance the Company's planned operations or the Company will reduce its costs, including curtailing its current plan to accelerate pursuit of U.S. clinical trials, in order to continue operating for the next 12 months.

Assuming we raise additional funds through the issuance of equity, equity-related or debt securities, these securities may have rights, preferences or privileges (including registrations rights) senior to those of the rights of our common stock and our stockholders will experience additional dilution.

Our independent registered public accounting firm has expressed substantial doubt about our ability to continue as a going concern.

As described in Note 1 of our accompanying financial statements, our auditors in their audit opinion have expressed concern with respect to our ability to continue as a going concern, as well as referred to Note 1 of our financial statements in this regard. Our financial statements do not include any adjustments that may result from the outcome of this uncertainty. If we cannot continue as a viable entity, our stockholders may lose some or all of their investment in us.

If our NurOwn treatment candidate does not demonstrate safety and efficacy sufficient to obtain regulatory approval, it will not receive regulatory approval and we will be unable to market it.

The therapeutic treatment development and regulatory approval process is expensive, uncertain and time-consuming. The timing of any future regulatory approval, if any, for our NurOwn treatment candidate cannot be accurately predicted. We do not expect to receive regulatory approval for any of our product candidates until at least 2015, if ever. If we fail to obtain regulatory approval for our NurOwn treatment candidate, we will be unable to market and sell it and we may never be profitable.

As part of the regulatory process, we must conduct clinical trials, including Phase 2 and Phase 3 clinical trials, for our NurOwn treatment candidate to demonstrate safety and efficacy in humans to the satisfaction of the FDA and regulatory authorities in other countries.

A failure of one or more of our clinical trials can occur at any stage of testing. Previous results obtained in uncontrolled clinical trials may not be predictive of future results obtained in controlled clinical trials. Interim results obtained in clinical trials may not be confirmed upon full analysis of the results of a clinical trial. Results of later stage clinical trials may fail to show the desired safety and efficacy despite acceptable results in earlier clinical trials. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses and many companies that have believed their product candidates performed satisfactorily in preclinical and clinical trials have nonetheless failed to obtain marketing approval of their treatments.

Specifically, we have not yet compared our NurOwn treatment candidate against placebo or any other active therapy control group. While comparisons of outcomes to results from other reported clinical trials can provide some insight into the efficacy of our NurOwn treatment candidate, there are many factors that affect the outcome of clinical trials, some of which are not apparent in published reports, and results from two different trials cannot always be reliably compared.

We are currently searching for a new Chief Executive Officer. If we were to unable to hire and retain an experienced and qualified CEO, we may experience difficulty executing our business strategy.

Our future success depends in a large part upon the continued service of key members of our senior management team. Alon Natanson, our former Chief Executive Officer, resigned from the Company effective October 28, 2013. Chaim Lebovits, our President, has assumed the duties and responsibilities of the Chief Executive Officer on an interim basis while we continue to search for a new Chief Executive Officer. Identifying and hiring an experienced and qualified Chief Executive Officer may be difficult for a small, development stage, biotech company such as ours. In particular, we expect that the CEO we hire will be critical to the overall management of the Company as well as the development of our technology, our culture and our strategic direction. If we are unable to hire and retain an experienced CEO or if we lose any other key members of our management or personnel we may not be able to execute our business strategy. We are currently searching for a new Chief Executive Officer and are deliberating over the candidates in order to hire the most qualified and best possible candidate.

Our business in the foreseeable future will be based on technology licensed from Ramot and if this license were to be terminated upon failure to make required royalty payments in the future, we would need to change our business strategy and we may be forced to cease our operations.

Agreements we and our Israeli Subsidiary have with Ramot impose on us royalty payment obligations. If we fail to comply with these obligations, Ramot may have the right to terminate the license under certain circumstances. If Ramot elects to terminate our license, we would need to change our business strategy and we may be forced to cease our operations. We currently do not owe Ramot any overdue payments. Royalties are due upon commencement of revenues by the Company.

Our company has a history of losses and we expect to incur losses for the foreseeable future.

As a development stage company, we are in the early stages of executing our business plan. We had no revenues for the fiscal years ended December 31, 2013 or December 31, 2012. Our ability to operate successfully is materially uncertain and our operations are subject to significant risks inherent in a developing business enterprise. We are currently in the process of introducing the Company to strategic partners. In the upcoming three years, the Company will focus on clinical trials. We are unable at this time to foresee when we will generate revenues from strategic partnerships or otherwise. Furthermore, we expect to incur substantial and increasing operating losses for the next

several years as we increase our spending to execute our development programs. These losses are expected to have an adverse impact on our working capital, total assets and stockholders' equity, and we may never achieve profitability.

Our product development programs are based on novel technologies and are inherently risky.

We are subject to the risks of failure inherent in the development of products based on new technologies. The novel nature of our stem cell therapy creates significant challenges with regard to product development and optimization, manufacturing, government regulations, and market acceptance. For example, the FDA has relatively limited experience with stem cell therapies. None have been approved by them for commercial sale, and the pathway to regulatory approval for our cell therapy product candidates may accordingly be more complex and lengthy. As a result, the development and commercialization pathway for our therapies may be subject to increased uncertainty, as compared to the pathway for new conventional drugs.

We are faced with uncertainties related to our research.

Our research programs are based on scientific hypotheses and experimental approaches that may not lead to desired results. In addition, the timeframe for obtaining proof of principle and other results may be considerably longer than originally anticipated, or may not be possible given time, resource, financial, strategic and collaborator scientific constraints. Success in one stage of testing is not necessarily an indication that the particular program will succeed in later stages of testing and development. It is not possible to predict, based upon studies in in-vitro models and in animals, whether any of the therapies designed for these programs will prove to be safe, effective, and suitable for human use. Each therapy will require additional research and development, scale-up, formulation and extensive clinical testing in humans. Unsatisfactory results obtained from a particular study relating to a program may cause the Company to abandon its commitment to that program or to the lead therapy or product candidate being tested. The discovery of unexpected toxicities, lack of sufficient efficacy, unacceptable pharmacology, inability to increase scale of manufacture, market attractiveness, regulatory hurdles, competition, as well as other factors, may make our targets, lead therapies or product candidates unattractive or unsuitable for human use, and we may abandon our commitment to that program, target, lead therapy or product candidate. In addition, preliminary results seen in animal and/or limited human testing may not be substantiated in larger controlled clinical trials.

If serious or unexpected adverse side effects are identified during the development of our NurOwn treatment candidate, we may need to abandon or limit its development.

If patients treated with our NurOwn treatment candidate suffer serious or unexpected adverse effects, we may need to abandon its development or limit development to certain uses or subpopulations in which these effects are less prevalent, less severe or more acceptable from a risk-benefit perspective.

The field of stem cell therapy is relatively new and our development efforts may not yield an effective treatment of human diseases.

Our intended cell therapeutic treatment methods for ALS involve a new approach that has not yet been proven to work in humans. We are currently conducting Phase IIa clinical trials for ALS, which, together with other stem cell therapies, may ultimately prove ineffective in treatment of human diseases. If we cannot successfully implement our NurOwn stem cell therapy in human testing, we would need to change our business strategy and we may be forced to change our operations.

Our NurOwn treatment candidate is based on a novel technology, which may raise development issues that we may not be able to resolve, regulatory issues that could delay or prevent approval or personnel issues that may keep us from being able to develop our treatments.

Regulatory approval of treatment candidates that utilize novel technology such as ours can be more expensive and take longer than for other treatments that are based on more well-known or more extensively studied technology, due to our and the regulatory agencies' lack of experience with them. This may lengthen the regulatory review process, require us to perform additional studies, including clinical trials, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of these treatment candidates or lead to significant post-approval limitations or restrictions. For example, the differentiated cell component of our NurOwn treatment candidate is a complex biologic product that is manufactured from the patient's own bone marrow that must be appropriately harvested, isolated, expanded and differentiated so that its identity, strength, quality, purity and potency may be characterized prior to release for treatment. No differentiated cell treatment for ALS has yet been approved for marketing by the FDA or any other regulatory agency. The tests that we use to make identity, strength, quality, purity and potency determinations on our NurOwn treatment candidate may not be sufficient to satisfy the FDA's expectations regarding the criteria required for release of products for patient treatment and the regulatory agency may require us to employ additional testing measures for this purpose, which could require us to undertake additional testing and/or additional clinical trials.

The novel nature of our NurOwn treatment candidate also means that fewer people are trained in or experienced with treatments of this type, which may make it difficult to recruit, hire and retain capable personnel for the research, development and manufacturing positions that will be required to continue our development and commercialization efforts.

A significant global market for our services has yet to emerge.

Very few companies have been successful in their efforts to develop and commercialize a stem cell product. Some stem cell products in general may be susceptible to various risks, including undesirable and unintended side effects, unintended immune system responses, inadequate therapeutic efficacy, or other characteristics that may prevent or limit their approval or commercial use. The demand for stem cell processing and the number of people who may use cell or tissue-based therapies is difficult to forecast. Physicians, patients, formularies, third party payers or the medical community in general may not accept or utilize any products that the Company or its collaborative partners may develop. Our success is dependent on the establishment of a large global market for our products and services and our ability to capture a share of this market.

We have limited experience in conducting and managing clinical trials and the application process necessary to obtain regulatory approvals.

Our limited experience in conducting and managing clinical trials and the application process necessary to obtain regulatory approvals might prevent us from successfully designing or implementing a preclinical study or clinical trial. Cell-based therapy products, in general, may be susceptible to various risks, including undesirable and unintended side effects, unintended immune system responses, inadequate therapeutic efficacy or other characteristics that may prevent or limit their approval by regulators or commercial use. Many companies in the industry have suffered significant setbacks in advanced clinical trials, despite promising results in earlier trials. If our clinical trials are unsuccessful, or if we do not complete our clinical trials, we may not receive regulatory approval for or be able to commercialize our product candidates.

If we do not succeed in conducting and managing our preclinical development activities or clinical trials, or in obtaining regulatory approvals, we might not be able to commercialize our product candidates, or might be significantly delayed in doing so, which will materially harm our business.

Our ability to generate revenues from any of our product candidates will depend on a number of factors, including our ability to successfully complete clinical trials, obtain necessary regulatory approvals and implement our commercialization strategy. We may, and anticipate that we will need to, transition from a company with a research and development focus to a company capable of supporting commercial activities and we may not succeed in such a transition.

We may not be able to secure and maintain research institutions to conduct our clinical trials.

We rely on research institutions to conduct our clinical trials. Our reliance upon research institutions, including hospitals and clinics, provides us with less control over the timing and cost of clinical trials and the ability to recruit subjects. If we are unable to reach agreements with suitable research institutions on acceptable terms, or if any resulting agreement is terminated, we may be unable to quickly replace the research institution with another qualified institution on acceptable terms. Furthermore, we may not be able to secure and maintain suitable research institutions to conduct our clinical trials.

We are subject to a strict regulatory environment. If we fail to obtain and maintain required regulatory approvals for our potential cell therapy products, our ability to commercialize our potential cell therapy products will be severely limited.

None of our product candidates have received regulatory approval for commercial sale. We do not expect to receive regulatory approval for any of our product candidates until at least 2015, if ever.

Numerous statutes and regulations govern human testing and the manufacture and sale of human therapeutic products in the United States and other countries where we intend to market our products. Such legislation and regulation bears upon, among other things, the approval of protocols and human testing, the approval of manufacturing facilities, testing procedures and controlled research, review and approval of manufacturing, preclinical and clinical data prior to marketing approval including adherence to GMP during production and storage as well as regulation of marketing activities including advertising and labeling.

The completion of the clinical testing of our product candidates and the obtaining of required approvals are expected to take several years and require the expenditure of substantial resources. We may experience numerous unforeseen events during, or as a result of, the clinical trial process that could delay or prevent regulatory approval and/or commercialization of our product candidates, including the following:

- The FDA or similar foreign regulatory authorities may find that our product candidates are not sufficiently safe or effective or may find our processes or facilities unsatisfactory;
- Officials at the Israeli MoH, the FDA or similar foreign regulatory authorities may interpret data from preclinical studies and clinical trials differently than we do;
- Our clinical trials may produce negative or inconclusive results or may not meet the level of statistical significance required by the Israeli MoH, the FDA or other regulatory authorities, and we may decide, or regulators may require us, to conduct additional preclinical studies and/or clinical trials or to abandon one or more of our development programs;
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The Israeli MoH, the FDA or similar foreign regulatory authorities may change their approval policies or adopt new regulations;

- There may be delays or failure in obtaining approval of our clinical trial protocols from the Israeli MoH, the FDA or other regulatory authorities or obtaining institutional review board approvals or government approvals to conduct clinical trials at prospective sites;
- We, or regulators, may suspend or terminate our clinical trials because the participating patients are being exposed to unacceptable health risks or undesirable side effects;
- We may experience difficulties in managing multiple clinical sites;
- Enrollment in our clinical trials for our product candidates may occur more slowly than we anticipate, or we may experience high drop-out rates of subjects in our clinical trials, resulting in significant delays; and
- We may be unable to manufacture or obtain from third party manufacturers sufficient quantities of our product candidates for use in clinical trials.

Investors should be aware of the risks, problems, delays, expenses and difficulties which may be encountered by us in light of the extensive regulatory environment in which our business operates. In particular, our development costs will increase if we have material delays in our clinical trials, or if we are required to modify, suspend, terminate or repeat a clinical trial. If we are unable to conduct our clinical trials properly and on schedule, marketing approval may be delayed or denied by the Israeli MoH or the FDA.

Even if a product candidate is approved by the Israeli MoH, the FDA or any other regulatory authority, we may not obtain approval for an indication whose market is large enough to recoup our investment in that product candidate. We may never obtain the required regulatory approvals for any of our product candidates. Later discovery of previously unknown problems with a product, manufacturer or facility may result in restrictions on the product or manufacturer, including a withdrawal of the product from the market.

Even if regulatory approvals are obtained for our product candidates, we will be subject to ongoing government regulation. If we or one or more of our partners or collaborators fail to comply with applicable current and future laws and government regulations, our business and financial results could be adversely affected.

The healthcare industry is one of the most highly regulated industries in the United States. The federal government, individual state and local governments and private accreditation organizations all oversee and monitor the activities of individuals and businesses engaged in the delivery of health care products and services. Even if regulatory authorities approve any of our human therapeutic product candidates, current laws, rules and regulations that could directly or indirectly affect our ability and the ability of our strategic partners and customers to operate each of their businesses could include, without limitation, the following:

- State and local licensing, registration and regulation of laboratories, the collection, processing and storage of human cells and tissue, and the development and manufacture of pharmaceuticals and biologics;
- The federal Clinical Laboratory Improvement Act and amendments of 1988;
- Laws and regulations administered by the FDA, including the Federal Food Drug and Cosmetic Act and related laws and regulations;
- The Public Health Service Act and related laws and regulations;
- Laws and regulations administered by the United States Department of Health and Human Services, including the Office for Human Research Protections;
- State laws and regulations governing human subject research;