Clinical study protocol

BCT-001-US

A PHASE 2, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED MULTICENTER STUDY TO EVALUATE SAFETY AND EFFICACY OF TRANSPLANTATION OF AUTOLOGOUS MESENCHYMAL STEM CELLS SECRETING NEUROTROPHIC FACTORS IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

Brainstorm Cell Therapeutics Ltd.
12 Bazel St., POB 10019,
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Israel 49001

Clinical study protocol [BCT-001-US]

PROTOCOL TITLE	A PHASE 2, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED MULTICENTER STUDY TO EVALUATE SAFETY AND EFFICACY OF TRANSPLANTATION OF AUTOLOGOUS MESENCHYMAL STEM CELLS SECRETING NEUROTROPHIC FACTORS IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS
PROTOCOL NUMBER	BCT-001-US
STUDY DESIGN (PHASE)	Phase 2
PROTOCOL DATE/VERSION	September 23, 2014/Amendment 1
IND NUMBER	IND 15878
Investigational Product	Autologous mesenchymal stem cells secreting neurotrophic factors (MSC-NTF, NurOwn™)
INDICATION	Amyotrophic Lateral Sclerosis (ALS)
SPONSOR	Brainstorm Cell Therapeutics Ltd. 12 Bazel St., POB 10019, Kiryat Aryeh, Petach Tikva, Israel 49001
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MEDICAL MONITOR	Kenneth J. Tack, MD PRC Clinical (810) 227-1386

Good Clinical Practices

This study will be conducted under Good Clinical Practices, in accordance with the Declaration of Helsinki, in compliance with the International Conference on Harmonization (ICH) guidelines.

CONFIDENTIAL

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PROTOCOL APPROVAL

A Phase 2 Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Transplantation of Autologous Mesenchymal Stem Cells Secreting Neurotrophic Factors in Patients with Amyotrophic Lateral Sclerosis; BCT-001-US.

Approved by:

Name	Title/Company	Signature	Date
Yael Gothelf, Ph.D.	VP Regulatory Affairs Brainstorm Cell Therapeutics	Y. Gothelf	23 Sept 2014
Anthony Fiorino, MD, PhD	CEO, Brainstorm Cell Therapeutics		9/28/2014
Dale W. Usner, Ph.D.	VP Biostatistics and Data Management, SDC		
Kenneth J. Tack, MD	Medical Monitor, PRC Clinical		

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Kenneth J. Tack, MD	Medical Monitor, PRC Clinical	Kenneth J. Tack	24Sept2014

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INVESTIGATOR'S AGREEMENT

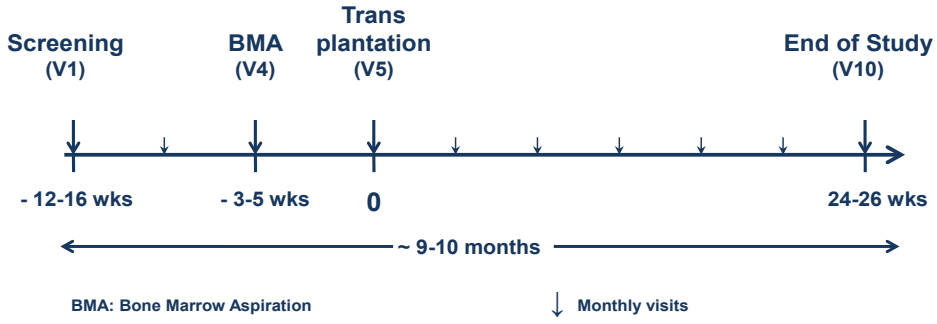
I have received and read the Clinical Protocol BCT-001-US, for BrainStorm Cell Therapeutics' MSC-NTF cells. I have read the protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Printed Name of Investigator

Signature of Investigator

Date

STUDY SYNOPSIS

Name of Sponsor	Brainstorm Cell Therapeutics Ltd. 12 Bazel St., POB 10019, Kiryat Aryeh, Petach Tikva, Israel 49001
Investigational Product	MSC-NTF cells
Indication	Amyotrophic Lateral Sclerosis (ALS)
Title of Study	A Phase 2 Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Transplantation of Autologous Mesenchymal Stem Cells Secreting Neurotrophic Factors in Patients with Amyotrophic Lateral Sclerosis
Protocol Date/Version	September 23, 2014/Amendment 1
OBJECTIVES	
Primary: To evaluate the safety of transplantation of expanded autologous MSC-NTF cells administered on a single occasion via combined intrathecal (IT) administration and 24 intramuscular (IM) injections given into the right biceps and triceps muscles in patients with ALS. Secondary: To compare the change in slopes from the pre-transplantation period to the post-transplantation period in ALSFRS-R between the treatment and placebo groups through 24 weeks post-transplantation. To compare the change in slopes from the pre-transplantation period to the post-transplantation period in SVC between the treatment and placebo groups through 24 weeks post-transplantation. To compare the slope of the rate of decline in the ALSFRS-R at 24 weeks following transplantation relative to the 12-16 week baseline period before transplantation in all patients (both treatment and placebo groups). To compare the slope of the rate of decline in SVC at 24 weeks following transplantation relative to the 12-16 week baseline period before transplantation in all patients (both treatment and placebo groups).	
METHODOLOGY	
Study Design	This is a Phase II randomized, double blind, placebo controlled multicenter study that will be conducted in 48 patients with early ALS (ALSFRS-R scores of ≥30) at up to 3 study sites. After providing informed consent, each patient will undergo approximately 12-16 week baseline period during which monthly ALSFRS-R scores and SVCs will be obtained. During this period of time their bone-marrow will be harvested and mesenchymal stromal cells will be isolated and expanded. Twelve to 16 weeks after screening, patients will undergo transplantation with their autologous MSC-NTF or matching placebo; product will be administered both intrathecally as well as intramuscularly as 24 IM injections given into the right biceps and triceps muscles, all at a single study visit. Following treatment they will have up to six monthly visits at which the ALSFRS-R and SVC will be obtained, along with vital signs, laboratory tests and recording of concomitant medications and adverse events (AEs, see scheme below). 
Treatments	Administration of MSC-NTF cells given intrathecally and via multiple intramuscular injections on a single occasion.

Treatment Duration	Each participant will be followed-up for three months pre-and six months post transplantation; thus, each participant's study participation will last for approximately 9 months. The expected study duration (taking into account the limitations of the manufacturing site which is expected to be able to process approximately 2-4 patients per month), the entire study duration is expected to be approximately 12-16 months.
Study Drug and Formulation	Study drug will be supplied in: • Twenty four 1ml syringes, each containing 2 x10^6 MSC-NTF cells in 200 µl (10 x10^6 cells/mL) or the same number of syringes containing placebo for IM administration. • One 5 ml syringe containing 4 ml of MSC-NTF cell suspension at a dose of 100-125 x10^6 cells or a 5 ml syringe containing placebo for IT administration.
Dose and Route of Administration	Study drug is to be delivered by IM and IT administration. The MSC-NTF cell dose is: • 100-125 x10^6 cells by IT administration • 48 x10^6 cells by IM administration. • Participants randomized to placebo will receive both IT and the same number of IM injections.
Concomitant and Excluded Therapy	Study participants will be on a stable dose of riluzole for at least 30 days prior to screening or not taking riluzole at all, nor plan to begin riluzole during the study period.
SUBJECT POPULATION	
Number of Subjects Planned	48 total (3:1 randomization with 36 subjects in the active treatment arm and 12 in the placebo arm).
Major Inclusion Criteria	Age 18 to 75 years old. ALS symptom onset defined as first onset of weakness ≤ 24 months and ALSFRS-R ≥30 at the Screening Visit. Upright slow vital capacity (SVC) measure ≥65% of predicted for gender, height, and age at the Screening Visit.
ASSESSMENTS	
Safety	Tabulation of AEs, changes in physical and neurological examination findings, hematology, serum chemistry, urinalysis, vital signs and requirement of concomitant medications.
Efficacy	The change in slope from the pre-transplantation period to the post-transplantation period in ALSFRS-R scores and slow vital capacity (SVC) through Weeks 12 and 24 post-transplantation for treatment compared to placebo. The change in slope from the pre-transplantation period to the post-transplantation period in ALSFRS-R scores and slow vital capacity (SVC) through Weeks 12 and 24 post-transplantation for each treatment group. The change in slope from the pre-transplantation period to the post-transplantation period in hand held dynamometry (HHD) and EIM (optional) through Weeks 12 and 24 post-transplantation for treatment compared to placebo. The change in slope from the pre-transplantation period to the post-transplantation period in hand held dynamometry (HHD) and EIM (optional) through Weeks 12 and 24 post-transplantation for each treatment group.
For the Schedule of Study Assessments, see Table 1 in Appendix 1.	

STATISTICAL METHODS AND ANALYSIS	
Efficacy	All efficacy analyses will use one-sided alpha = 0.10 tests and present one-sided 90% lower confidence limits and two-sided 95% confidence intervals around the difference between treatments as well as two-sided 95% confidence intervals around the point estimates within each treatment group. All summaries will be presented by treatment group. Secondary Objectives: The change in slope from pre-transplantation to post-transplantation in ALSFRS-R and in SVC (as a percent of normal for age and sex) will be estimated using the mixed linear statistical model. The fixed effect variables in the model will be: • Visit, expressed in days from the beginning of treatment (i.e. pre-treatment times will have negative values, post-treatment times positive values); • Treatment; • Two-way interactions between visit & post-treatment indicator, (0 for pre-treatment visits, 1 for post-treatment visits) and visit & treatment; • Three-way interaction between visit & post-treatment visit indicator & treatment; • Site. The repeated measures within a subject over visit will also be accounted for in the model, wherein the covariance structure will be evaluated using Bayesian information criterion (BIC). Covariance structures to be evaluated are: unstructured, toeplitz, spatial power with day, and compound symmetry. The three-way interaction between visit & post-treatment visit indicator & treatment will be used to compare the change in slope in the treatment group to the change in slope in the placebo group. The post-pre slope estimate for the active treatment group will be used to test the change from pre-transplantation to post-transplantation within the active treatment group. Exploratory Objectives: The analysis for EIM (optional) and HHD will employ the same modeling approach as described above for the secondary objectives. The analysis for HHD will be based on a combined score reflecting muscles in the right arm. A further analysis of HHD will compare the score for the right arm to the score for the left arm. The linear mixed model will include, in addition to the terms described above, an indicator for "right arm", interactions between that indicator and all other variables in the model, and a random effect term for the right arm indicator.
Safety	The proportion of subjects having each AE will be compared between treatment groups using Fisher's exact tests. When evaluating changes in safety parameters, baseline will be defined as the last measurement prior to transplantation (i.e., prior to treatment). Physical examination, neurological examination, hematology, serum chemistry, vital signs, ECG and concomitant medications will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) if the data is continuous and using counts and percentages if the data is discrete. Shifts from baseline in categorization of results (e.g. normal/abnormal or low/normal/high) will also be summarized.

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ABBREVIATIONS

ADL	Activities of Daily Living
AE	Adverse Event
ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	ALS Functional Rating Scale –Revised
ALT	Alanine aminotransferase (alanine transaminase)
AST	Aspartate aminotransferase (aspartate transaminase)
BDNF	Brain Derived Neurotrophic Factor
CBC	Complete Blood Count
CRF	Case Report Form
CSF	Cerebral Spinal Fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DMEM	Dulbecco Modified Eagle Medium
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EIM	Electrical Impedance Myography
FAS	Full Analysis Set
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GDNF	Glial Derived Neurotrophic Factor
HBSS	Hank's Balanced Salt Solution
HGF	Hepatocyte Growth Factor
HHD	Hand Held Dynamometry
IGF-1	Insulin-like Growth Factor 1
IM	Intramuscular
IRB	Institutional Review Board
IT	Intrathecal
LP	Lumbar Puncture
MedDRA	Medical Dictionary for Regulatory Activities
MN	Motor Neuron
MOH	Israel Ministry of Health
MSC	Mesenchymal Stromal Cells
MSC-NTF	Mesenchymal Stromal Cells secreting Neurotrophic Factors
NTF	Neurotrophic Factors
PP	Per Protocol
PT	MedDRA Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SNI	Sciatic Nerve Injury

SOA	Schedule of Activities
SOC	MedDRA System Organ Class
SOD	Superoxide dismutase 1
SVC	Slow Vital Capacity
TEAE	Treatment-Emergent Adverse Event
VEGF	Vascular Endothelial Growth Factor

6. CLINICAL STUDY PROTOCOL

6.1. INTRODUCTION

6.1.1. Background

Amyotrophic lateral sclerosis (ALS) is a fatal neurological disease. There is currently no available treatment to stop or reverse its progressive course. There remains an unmet medical need for safe and effective treatments for people with ALS.

Based on putative pathophysiologic mechanisms, there are several therapies under investigation such as anti-glutamatergic agents, drugs targeting protein misfolding and accumulation, antioxidant therapy, immunomodulatory agents, and stem cell transplantation.

Cyto-therapy may hold the key to circumventing multiple hurdles in the ALS pathophysiological cascade (Morren JA et al. 2012). Apart from the replacement of lost or damaged motor neurons, stem cell implantation therapy may benefit ALS patients by an independent effect of cytoprotection. Experimental data has shown that non-neuronal cell replacement can be a strategic therapy in promoting motor neuron survival and improved neuromuscular function (Corti S et al. 2010).

Neurotrophic factors secreting mesenchymal stromal cells (MSC-NTF) cells are a novel cell-therapeutic approach which aims to effectively deliver NTF directly to the site of damage in ALS patients.

The MSC-NTF cell therapy (NurOwn) is based on transplantation of autologous bone marrow derived mesenchymal stromal cells (MSC), which are enriched from the mononuclear fraction of the patients' own bone marrow, propagated *ex vivo* and induced to secrete NTF such as Glial Derived Growth Factor (GDNF) and Brain Derived Growth Factor (BDNF), Vascular Endothelial Growth Factor (VEGF) and Hepatocyte growth factor (HGF). These cells are thus designated MSC-NTF cells.

The autologous MSC-NTF cells are back-transplanted into the ALS patient into the sites of damage, the spinal cord and/or the muscles, where axon terminals will take up the neurotrophic factors secreted by the transplanted cells. In the muscles, the transplanted cells are close to the motor-end plates at the axon terminals, and in the spinal cord the cells are close to the cell bodies. Axon terminals take up the NTF and transport them retrogradely along the axons into the neuron cell bodies, thus aiming to prevent further degeneration of the neuronal cells.

NTFs are potent survival factors for embryonic, neonatal, and adult neurons and are considered potential therapeutic candidates for ALS. Delivery of appropriate NTFs to the immediate environment of afflicted neurons in ALS patients is expected to improve their survival and thus slow down disease progression and alleviate symptoms.

6.1.2. Summary of Previous Clinical Experience with MSC-NTF cell transplantation

An open-label, two patient-group Phase 1/2 trial of MSC-NTF in 12 people with ALS, has been recently completed at the Hadassah Medical Center in Jerusalem, Israel (ClinicalTrials.gov Identifier: NCT01051882).

In this first study, six participants with early stage ALS disease received intramuscular (IM) injections of MSC-NTF, and six patients with more progressive disease received MSC-NTF by intrathecal (IT) administration. The six participants with early-stage ALS received an IM dose of ~1 x 10^6 MSC-NTF cells/site into 24 sites along the biceps and triceps muscles of the right arm for a total of ~24x10^6 cells/patient, and those with more advanced disease received an IT dose of 1x10^6 MSC-NTF cells per Kg of body weight for a total of ~60x10^6cells/patient (see table below).

Patient group	Number of patients	Route of Administration	# of injection sites	Site of Administration	Dose
Early stage	6	Intramuscular (IM)	24	Biceps and triceps muscles	1 x 10^6 cells/site
Advanced stage	6	Intrathecal (IT)	1	Cerebrospinal fluid (CSF)	1 x 10^6 cells/kg body weight

The interim safety report for the first 12 patients in the Phase 1/2 clinical trial, submitted to the Israel Ministry of Health (MOH), indicated that MSC-NTF cells treatment, either by IM or IT administration was generally well tolerated for 6 months. No treatment-related adverse events (AE) were reported in the 12 patients treated by either route of administration.

In this study a trend towards a decreased rate of decline on ALSFRS and FVC efficacy measures in the IT treated patients over 6 months post-transplant as compared to the three months pre-transplant follow-up was observed.

A Phase 2a dose-escalating study is currently ongoing at the Hadassah Medical Center in Jerusalem, Israel.

The Phase 2a study is designed to determine the safety and preliminary effects on outcome measures of MSC-NTF administered by combination treatment of intramuscular and intrathecal administration, in three cohorts of 4 early-stage ALS patients, receiving increasing doses of MSC-NTF cells. The first group of patients received a combination treatment of the current dose, the second group of patients received a 1.5 fold combination treatment of the current dose and the third group of patients received a 2 fold combination treatment of the current dose (see table below).

Dose	Low	Medium	High
Number of patients	4	4	4
IM Dose (cells/site)	1x 10^6	1.5x 10^6	2 x 10^6
IT Dose (cells/kg body weight)	1 x 10^6	1.5 x 10^6	2 x 10^6
Total dose	~ 94 x 10^6	~ 141 x 10^6	~ 188 x 10^6

All participants will be followed for 3 months before and 6 months after transplantation. This study will provide important safety and dosing data as well as preliminary assessment

of the effects of MSC-NTF on ALS relevant outcome measures (ClinicalTrials.gov Identifier: NCT01777646).

An interim safety summary report for the first 12 patients in the study was submitted to the Hadassah Medical Center Ethical Committee about two month after transplantation of the 12^{th} patient. One SAE (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.

Four compassionate use ALS patients have been treated with MSC-NTF cells with no apparent safety related concerns.

The first compassionate use ALS patient was treated by IT transplantation of 1 x 10^6 cells/kg body weight autologous MSC-NTF cells. During the 5 months follow up, no treatment-related adverse effects had been reported.

The second compassionate use ALS patient received a combination of IT and IM injections of autologous MSC-NTF cells: 1 x 10^6 cells/kg body weight IT and 1x10^6 cells/site in 24 sites, IM. No significant treatment-related adverse effects had been reported observed during the 9 months post-transplantation follow-up. The follow-up report for this patient is attached hereto.

The third compassionate use patient (diagnosed with both ALS and myasthenia gravis) received a higher combination dose of IT and IM injections of autologous MSC-NTF cells, namely 1.5 x 10^6 cells/kg body weight IT and 1.5 x 10^6 cells/site in 24 sites IM for a total of 147 x 10^6 MSC-NTF cells. During the 2 months follow-up no significant side effects were observed. This compassionate use patient showed an improvement in the ALSFRS-R score, in muscle power (muscle chart) and in the respiratory parameters (FVC).

This patient was subsequently re-treated 5 months after the first injection with a second dose of MSC-NTF cells. Two months after repeated MSC-NTF transplantation all neurological functions were found to have improved. A case report for this patient entitled 'Rare Combination of Myasthenia and ALS, Responsive to NTF-MSC Stem Cell Therapy' was recently accepted for publication in 'Muscle and Nerve'.

No formal assessment was performed for the repeated treatment of this compassionate treated patient, or for the fourth compassionate treated patient. Brainstorm Cell Therapeutics has not received any reports from the treating physicians of any adverse effects suspected to be due to the product in these four patients.

In this proposed Phase 2 study, our goal is to evaluate the safety of MSC-NTF cells and their effect on several widely used, validated outcome measures in ALS. The MSC-NTF cells will be administered by combined IM and IT routes of administration; the doses being proposed in this study represent the highest doses that were administered in the previous clinical studies; in those studies and in the compassionate use patients, these doses appeared to be generally well-tolerated by the 28 subjects to whom they were administered.

6.1.3. Summary of Relevant Nonclinical Experience with MSC-NTF

6.1.3.1. The Role of Neurotrophic Factors in ALS

Neurotrophic factors (NTF) are small, naturally occurring polypeptides that support the development and survival of neurons. NTF are reported to be potent survival factors for embryonic, neonatal, and adult neurons and studies in ALS animal models have shown a delay in disease onset and/or progression after administration of various neurotrophic factors. Therefore, NTF are considered potential therapeutic candidates for ALS as well as for other neurodegenerative diseases.

Several studies in peripheral nerve injury have shown that NTFs play an important role in the development, maintenance and regeneration of the nervous system. BDNF was shown to prevent the loss of motor units and to contribute to the maintenance of muscle mass when administered to the hind limb muscles of mice after neonatal peripheral nerve injury (Mousavi K et al., 2004). In addition BDNF enhances branching and arborization of Corticospinal motor neurons (Ozdinler PH et al., 2006). GDNF and Insulin Growth Factor 1 (IGF-1) are two of the most potent survival factors known for peripheral neurons. Several studies have shown that GDNF and IGF-1 can prevent neuronal degeneration in mice and rats after axotomy, as well as the programmed cell death of motor neurons during development (Henderson, CE, et al. 1994, Mohajeri H et al. 1999, Wang, LJ et al. 2002, Acsadi G et al. 2002, Ozdinler PH et al. 2006, Suzuki M et al. 2008).

The ability of growth factors to protect dying motor neurons has also been extensively studied in ALS models of disease.

A variety of preclinical and clinical studies already suggest that local delivery of vascular endothelial growth factor (VEGF) has neurotrophic and neuroprotective effects for ALS. The VEGF family, which includes factors that are primarily associated with angiogenesis are now increasingly recognized to have neurotrophic effects.

Reduced expression of a member of this family, VEGF-A, in mice results in neurodegeneration similar to that of ALS, while treatment of animal models of ALS with either VEGF-A gene therapy or VEGF-A protein has yielded positive therapeutic outcomes. These basic research findings raise the potential for a VEGF therapy to be translated to the clinic for the treatment of ALS (Reviewed Keifer et al 2013).

Increased expression of VEGF by intramuscular viral injections prolongs their survival and enhances motor performance (Azzouz, M et al. 2004, Zheng, C et al. 2004). Intracerebroventricular administration of VEGF in a rat model of ALS enhanced motor neuron survival, whereas an intraperitoneal injection of VEGF led to the preservation of neuromuscular connections (Storkebaum, E, et al., 2005). Moreover, a recent study indicates that intramuscular administration of a VEGF zinc finger transcription factor activator, which can induce VEGF expression, improves motor functions in SOD1-G93A rats (Kliem, MA, et al., 2011).

A recent study has shown that hMSC engineered to express GDNF and VEGF synergistically significantly prolonged survival and slowed the loss of motor function in a rat model of ALS (Krakora D. et al. 2013).

Hepatocyte growth factor (HGF) was first identified and molecularly cloned as a potent mitogen for mature hepatocytes (Nakamura et al., 1984, 1989).

Hepatocyte growth factor (HGF) is also a potent in vitro and in vivo survival-promoting factor for neurons (Kadoyama K, et al. 2007). HGF was first identified and molecularly cloned as a potent mitogen for mature hepatocytes (Nakamura et al., 1984, 1989).

Subsequent studies revealed that HGF exerts multiple biological effects (c-Met) (Funakoshi and Nakamura, 2003).

Neurotrophic effects of HGF have been demonstrated in vivo on embryonic spinal motor neurons during development and on adult motor neurons after axotomy of the hypoglossal nerve (Novak KD et al. 2000). Overexpression of neuronal HGF has been shown to result in the attenuation of neuronal cell death and progression of disease in a familial ALS transgenic mouse model (Sun W et al. 2002). Introduction of the HGF gene into neurons of transgenic mice expressing human mutant Cu⁄Zn superoxide dismutase (G93A mice) attenuates motor neuron degeneration and increases the life span of these mice. (Sun W et al. 2002).

6.1.3.2. In vitro protection of motorneurons by MSC-NTF cells

In order to test whether MSC-NTF cells are capable of rescuing motoneurons, we examined the effects of conditioned media of the MSC-NTF cells on a motoneuron cell line (NSC-34, Cashman NR et al. 1992). We found that the conditioned medium protects from NO damage (induced by SIN-1), glutamate toxicity, H_2O_2 (Sadan O et al.2009, Yust-Katz S et al. 2012) and hypoxia (Fig. 1) suggesting that soluble factors secreted from MSC-NTF cells may protect motor neurons from the damage associated to the pathophysiology of ALS.

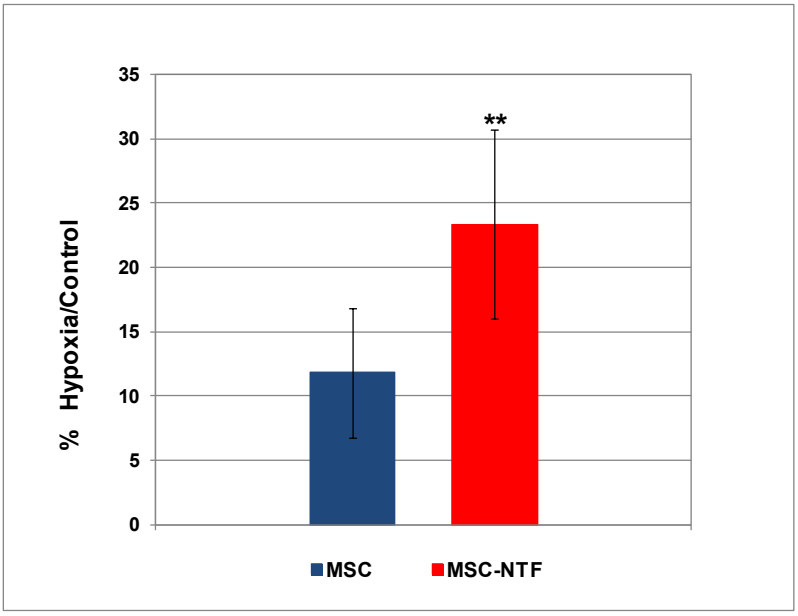

Figure 1: MSC-NTF cells' conditioned medium protects motorneuron cells from hypoxia.

Motorneuron cells (NSC 34) were exposed for 48hrs to hypoxia (1% H_2, 4% CO_2 and 95%N_2) in the presence of conditioned medium of MSC-NTF cells or of MSC. Cell viability was measured by Alamar Blue (O.D., 544-590 nm) and the ratio between hypoxia and control (with no Hypoxia) for each conditioned medium was calculated. MSC-NTF conditioned medium is shown to be significantly more protective as compared to MSC conditioned medium against hypoxic stress ($p<0.001$, $n=20$).

6.1.3.3. MSC-NTF secreting cells improve motor function and increase survival of SOD1 mice

Aiming to evaluate the effect of autologous transplantation of mouse MSC-NTF cells in a mouse model of ALS, we used mouse bone marrow derived mesenchymal stem cells that were induced to differentiate and secrete NTF. MSCs isolated from mice and induced to differentiate into NTF secreting cells, demonstrated similar phenotype and characteristics as the human MSC and MSC-NTF cells respectively. The MSC-NTF cells ($5x10^5$) were transplanted into the cerebral ventricle and into the leg muscles ($5x10^5$) of Superoxide dismutase 1 (SOD1) transgenic mice. We found that, compared to control (saline) injected mice, the cell-transplanted mice performed better on rotarod, had delayed onset of the disease and an extended life span. Additionally the life span of the MSC-NTF treated SOD1 mice increased by 18.8 days as compared to saline injected SOD1 mice (151.8 *vs*. 133 days, $p<0.007$, Fig. 2).

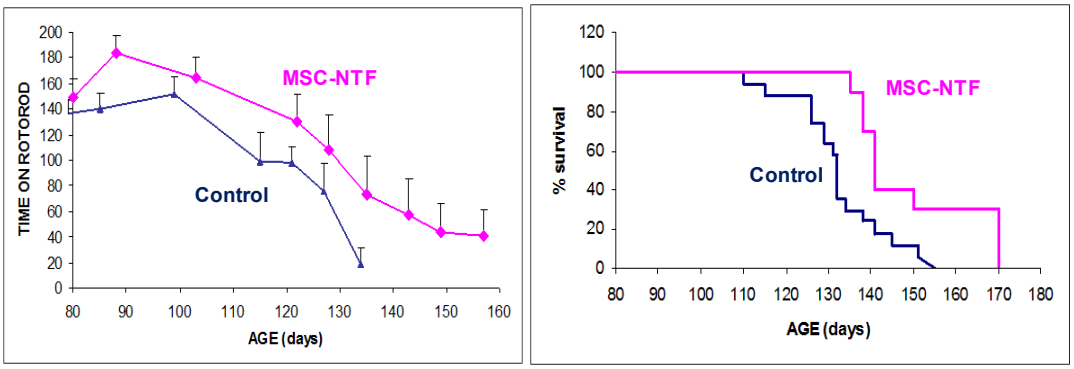

Figure 2: Transplantation of MSC-NTF cells improved the symptoms and the survival in a mice model of ALS.

SOD1 transgenic mice were transplanted with MSC-NTF cells (10^6) into the cerebral ventricle and into the leg muscles. The motor function was evaluated by rotarod (left panel). The survival curve shows the death rate of the treated and the saline control mice (right panel).

6.1.3.4. Therapeutic Effects of Differentiated Mesenchymal Stem Cells in a Rat Model of Sciatic Nerve Injury

Motor neuron (MN) loss is the origin of several fatal, progressive neurodegenerative diseases including ALS (Boillée et al., 2006). It is characterized by a progressive loss of MNs from the spinal cord, brainstem, and cerebral cortex.

Sciatic nerves are the longest and largest single nerves in the body. They begin in the lower spinal cord and run through the pelvis and down the lower limb. The sciatic nerves innervate the back of the thigh, leg and foot muscles.

Since the sciatic nerve supplies movement to most of the lower limb, damaging this motor system, models lower limb paralysis and the deficits that occur in diseases like ALS. While the etiologies of ALS and lower limb paralyses differ, the clinical presentations have similarities, and both lack effective treatments.

It has been shown that the retrograde death of motor neurons in the adult spinal cord after sciatic nerve avulsion is due to apoptosis (Martin LJ et al. 1999). Since retrograde

degeneration and neuronal apoptosis may participate in the mechanisms for motor neuron death in ALS it is suggested that this model can provide important information toward the understanding of motor neuron protection in ALS.

The protective effect of autologous MSC-NTF cells was studied in the sciatic nerve injury model in rat as a model for motorneuron damage which is representative of the damage seen in ALS (Dadon-Nachum M et al 2011a).

We examined whether MSC-NTF cells are capable of rescuing motor neurons in a unilateral Sprague-Dawley rat Sciatic Nerve Injury (SNI) model. The right hind limb sciatic nerve was crushed for 30 seconds in two points above the first branching of the nerve using a clamp. One day later, rats were transplanted with rat MSC-NTF cells or control into the site of the lesion. Four days after transplantation, in rats injected with the MSC-NTF cells, motor function measured by rotarod was found to be markedly preserved (73% vs. control in the MSC-NTF cells treated rats as compared to 41% in the control-injected group, $p<0.01$).

These finding indicate that intramuscular transplantation of autologous MSC-NTF cells rescued neuron damage in the sciatic nerve injury in rats and therefore support the notion that MSC-NTF can protect and increase restoration of motor-neurons, the cell population that suffers the most damage in ALS (Dadon-Nachum M et al 2011).

6.1.4. MSC-NTF Benefit and Risk Assessment

ALS is a fatal neurological disease. There is currently only one product approved for the treatment of ALS, namely, riluzole, which was demonstrated to increase time to tracheostomy or death in patients randomized to riluzole compared to those randomized to placebo. No other products have been approved for the treatment of ALS since riluzole's approval in 1995. Thus, there remains a great unmet medical need for safe and more effective treatments for people with ALS.

Most of the current investigational therapies in development for ALS, such as anti-glutamatergic agents, drugs targeting protein misfolding and accumulation, antioxidant therapy and immunomodulatory agents, focus on one of multiple putative pathophysiologic mechanisms.

Cyto-therapy may hold the key to circumventing multiple hurdles in the ALS pathophysiological cascade (Morren JA et al. 2012). Apart from the replacement of lost or damaged motor neurons, stem cell implantation therapy may benefit ALS patients by an independent effect of cytoprotection.

Experimental data have shown that non-neuronal cell replacement can promote motor neuron survival and improved neuromuscular function (Corti S et al. 2010).

Preclinical studies in several animal models of neurodegenerative diseases have shown benefits of MSC-NTF transplantation, which support the evidence that these cells may be effective treatment of ALS patients.

Autologous MSC-NTF transplantation appears to be generally safe in the 28 ALS patients in whom the product has been administered in two open-label GCP compliant clinical trials as well as in five treatments in 4 patients with ALS in which the cells were administered on a "compassionate" basis treatment.

In the open-label studies we previously conducted, no serious treatment-related adverse events were reported in the 12 treated ALS patients who were administered the product via either IM or the IT route of administration or in the 12 patients that received a combined IT and IM administration of increasing doses of MSC-NTF cells (See section 6.1.2).

The dose for the proposed Phase 2 study is the highest IM and IT combined administration dose, found to be well tolerated in the Phase 2a clinical study and in the 'compassionate use' treated patients.

In our previous study a trend towards a decreased rate of decline on the ALSFRS-R and on FVC was observed in the IT treated patients over 6 months post-transplant as compared to the three months pre-transplant follow-up, suggesting that the product should be further evaluated in this indication.

MSC are plastic-adherent cells isolated from the mononuclear fraction of the bone marrow. The bone marrow compartment is a convenient source for MSC.

In summary, autologous transplantation of adult bone marrow-derived MSC offers practical advantages since:

- Bone marrow cells can be easily and safely obtained by needle aspiration. Although the crude bone marrow contains only very low numbers of MSC ($1:10^4$-10^5), they can be enriched and expanded *ex-vivo* from the bone marrow mononuclear cell fraction.
- There is no need for immunosuppression since rejection is not expected when autologous MSC are administered.

Potential risks of participation in this study are considered to be low, and include the following:

- Risks associated with bone marrow harvesting and related conscious sedation
- Risks of LP include post-LP headache and CSF leak that could potentially require treatment.
- Risks of IM administration may include local skin irritation at the injection sites.
- As this is an autologous treatment and there is variability between patients' cells' growth capabilities, there is also a possibility that patients' cells will not grow sufficiently and may not allow the required cell dose to be transplanted back.

Therefore, the potential benefits of IT and IM injections of MSC-NTFs justify the small risks associated with the harvesting of Bone Marrow and administration of this autologous product.

6.2. STUDY OBJECTIVES

6.2.1. Primary objective

To evaluate the safety of MSC-NTF transplantation via combined IT and IM injections in participants with ALS.

6.2.2. Secondary Objectives

To compare the change in slopes from the pre-transplantation period to the post-transplantation period in ALSFRS-R between the treatment and placebo groups through 12 and 24 weeks post-transplantation.

To compare the change in slopes from the pre-transplantation period to the post-transplantation period in SVC between the treatment and placebo groups through 12 and 24 weeks post-transplantation.

To compare the slope of the rate of decline in the ALSFRS-R at 12 and 24 weeks following transplantation relative to the 12-16 week baseline period before transplantation in all patients (both treatment and placebo groups).

To compare the slope of the rate of decline in SVC at 12 and 24 weeks following transplantation relative to the 12-16 week baseline period before transplantation in all patients (both treatment and placebo groups).

6.2.3. Exploratory Objectives

To compare the slopes of decline of hand-held dynamometry (HHD), and electrical impedance myography (EIM, for patients in whom this optional outcome measure is available) against placebo as well as during the 12-16 week pre-transplant monitoring period relative to the 24 week post-transplant follow-up period.

Determine feasibility of succeeding in blinding patients and caregivers to the treatment, in anticipation of a requirement to include the placebo group in the Phase III efficacy study.

To examine the CSF of ALS patients at baseline and two weeks after treatment for the presence of neurotrophic factors and possible ALS biomarkers.

6.3. INVESTIGATIONAL PLAN

6.3.1. Overall Study Design and Plan

This is the third clinical study of autologous MSC-NTF cells conducted by BrainStorm Cell Therapeutics and the first study conducted under this IND in the U.S. It is a Phase II randomized, double blind, placebo controlled multicenter study that will be conducted in 48 patients with early ALS (ALSFRS-R scores of ≥30) at up to 3 US study sites. After providing informed consent, each patient will undergo a 12-16 week baseline period during which monthly ALSFRS-R scores and SVCs will be obtained. During this period of time their bone-marrow will be harvested and deriving mesenchymal stromal cells will be expanded. Twelve to 16 weeks after screening, patients will undergo transplantation with their autologous MSC-NTF or matching placebo; product will be administered both intrathecally as well as intramuscularly as 24 IM injections given into the right biceps and triceps muscles, all at a single study visit. Following treatment they will have monthly visits at which the ASLFRS-R and SVC will be obtained, along with vital signs, laboratory tests and recording of concomitant medications and AEs.

All participants will undergo informed consent and sign a written informed consent document. Participants will be informed that in case their autologous bone marrow fails to grow adequate numbers of MSC they will not receive the transplant. All participants will be observed for a total of 12-16 weeks prior to undergoing a bone marrow aspiration

procedure to establish each individual's rate of progression over a total of about 3 months to be compared to post-treatment measures. This pre-treatment period also includes about four weeks of the cell propagation (see Figure 3).

The 48 participants will be randomized (3:1) into a treatment or into a placebo group which will occur at Visit 3. Cells from the treatment group participants will be propagated in a cell culture facility over a period that can range from 24 to 38 days. Participants in both the treatment and placebo groups will then undergo combined IT and intramuscular (IM) injections (Figure 1). Both groups will be monitored for 24 weeks post-treatment. Participants in each group will be monitored by evaluators blinded to the treatment group, using identical procedures during the pre-transplantation period and for an additional 24 weeks post-treatment. Participants will be followed by in-person visits and telephone visits at least monthly throughout the trial (see schedule of activities (SOA) in Tables 1 and 2).

The autologous production process is on a per-patient basis and begins upon fresh bone marrow aspirate arrival to the cleanroom facility and is completed once the cells are ready for transplantation. Because the production capacity of the cell manufacturing facility is limited, it will be the limiting factor for the rate of enrolment. Based on the production capacity limitations, patients are expected to be recruited at a rate of approximately 2-4 patients/months throughout the trial.

6.3.2. Study Schematic

The study comprises a 12-16 week pre-treatment follow-up period and a 24 week post-treatment follow-up period (Figure 1).

Patient bone marrow will be aspirated about 9-11 weeks following the first screening visit. The MSC isolation and cell propagation process will last about 3-5 weeks and will be followed by MSC-NTF cells transplantation.

At the transplantation visit (about 12-16 weeks after the screening visit), subjects will be admitted to an inpatient study unit for study procedures and will be followed for 44-72 hours post transplantation.

Following treatment patients will be followed at monthly visits for a total of 24 weeks.

Each patient will thus be followed for a total of about 38 weeks (9-10 months) from the first screening visit (Figure 3).

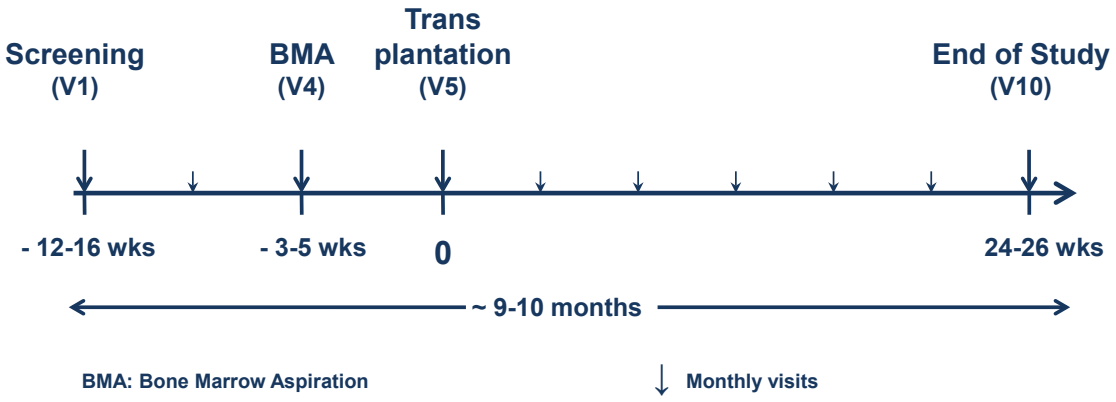

Figure 3: Clinical Study flowchart

Clinical study flowchart outlining the pre- and post-transplant follow-up.

6.3.3. Treatment Plan

6.3.3.1. Bone Marrow aspiration procedure:

Human bone marrow will be aspirated by a credentialed health care provider as per Medical Centre procedures bilaterally from multiple punctures of the iliac crest of the pelvic bone of patients into 20 mL syringes prefilled with approximately 1.5 mL of a Heparin-containing solution (Heparin Solution, USP, 100 units/mL) diluted 1:20 in HBSS.

Vacutainer tubes (Green cap 6 ml REF 367886 BD or equivalent with Sponsor approval) containing Lithium Heparin Sodium for injection (95 IU units/tube) will be pre-labelled and the cap pre-cleaned with Ethanol. After replacing the aspiration needle with a new sterile 19 gauge needle, the bone marrow aspirated from each single puncture (2-3 ml), will be injected into a separate pre-labelled Vacutainer tube. Immediately after bone marrow is injected into the tube, the tube will be thoroughly mixed to avoid clotting of the bone marrow sample.

A total of 50-70 ml of Bone Marrow will be aspirated from each patient.

6.3.3.2. IT Transplant Procedure

Participants will undergo a lumbar puncture (Spinal needle 20GA 3.50 IN (0.9 x 90 mm) followed by intrathecal injection of cells or placebo (Dulbecco modified Eagle Medium, DMEM). The detailed transplantation procedure is provided in Appendix 3.

6.3.3.3. IM Transplant Procedure

Participants will undergo a unilateral (right) IM transplantation of cells or of placebo solution (DMEM) into 24 sites in the biceps and triceps muscles of the upper arm (Figure 4). The detailed transplantation procedure is provided in Appendix 4.

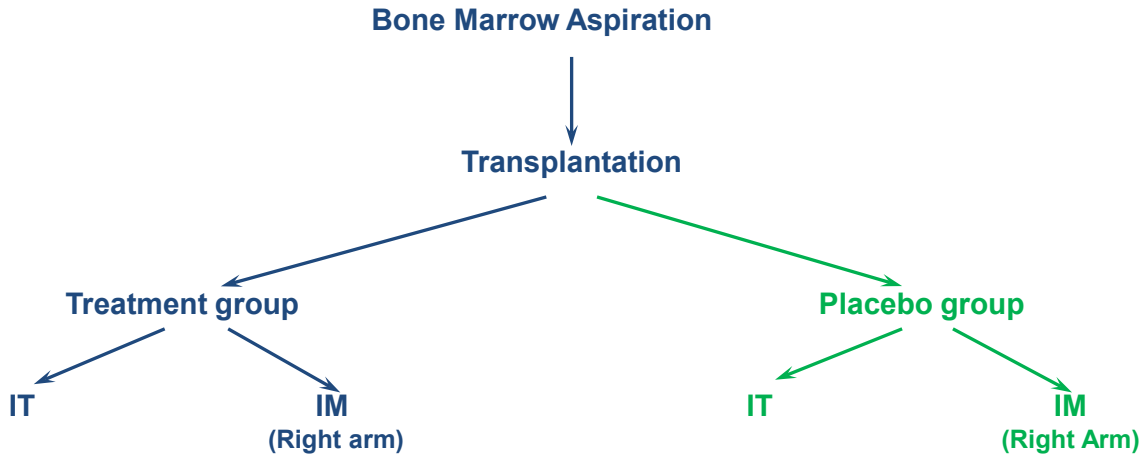

Figure 4: Study groups flowchart

Diagram delineating placebo and cells transplantation in the treatment and placebo groups.

6.3.4. Blinding and Randomization

Randomization will be used to avoid bias in the assignment of patients to treatment, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons.

This is a double-blind study; the investigators, the subjects, and designated study monitors will be blinded to the treatment assignment throughout the subject's participation in the trial. The exceptions to the blinding will be the Production team (unblinded personnel) at the cell culture facility at the site who distribute the MSC-NTF cells, and the unblinded statistician who will create the final randomization schedule but will not otherwise be involved in the trial.

Randomization will be stratified by site. Site-specific randomization lists will be provided to the Production manager prior to any subjects being randomized. The Production manager will refer to the randomization list when assigning treatment to a subject, and will allocate the treatment corresponding to the subject's randomization number. Randomization numbers will be assigned sequentially as subjects are randomized at each site. Randomization will occur at Visit 3 (one week before Bone Marrow aspiration) after eligibility has been confirmed. The subject's randomization number will be recorded in the subject's source documentation and CRFs, and the randomization number will be provided to the cell culture facility in preparation for the MSC isolation and cell propagation process.

In the event that emergency unblinding is necessary, the treatment codes for all subjects, where the treatment code information for each subject will be separated to ensure that all treatment codes will not be unblinded unnecessarily, will be available from the Medical Monitor. The randomization code may be broken only in the event of an emergency when it is essential to know which treatment the subject received in order to provide appropriate care. Whenever the code is broken for safety reasons, the date, time, and reason for unblinding must by documented by the investigator or any other person breaking the code, the Sponsor must be notified immediately.

6.3.5. Duration of study

Participants will be screened and undergo bone marrow aspiration after 9-10 weeks. Following aspiration, cells will be grown in culture for approximately 24-30 days (3-4 weeks). Participants in both the treatment and placebo groups will undergo combined IT and IM cell transplantation with either MSC-NTF cells or the placebo (DMEM). Following cell transplantation, participants will be monitored as inpatients for a period of at least 44 hours. Participants will be discharged after at least 44 hours and up to 72 hours unless a clinical adverse event(s) occur that require continued inpatient monitoring and/or treatment. Each subject's participation in the study will last for approximately 9 months.

6.3.6. Discussion of Dose

The combined IM and IT transplantation dose is the highest dose of MSC-NTF administered by combined intramuscular and intrathecal administration shown to have been safely administered in previous clinical trials in ALS patients (see section 6.1.2 above).

6.3.7. Discussion of Study Design, Including Choice of Control Group

The study is a randomized double blind placebo controlled study. The control group will be given placebo. It is expected that 36 subjects given MSC-NTF and 12 subjects DMEM in the placebo arm will provide an adequate number of subjects to compare rates of adverse events between the treatment and control groups and allow us to explore the effects on the rates of decline on the ALSFRS-R and SVC between the treatment and placebo control groups as well as individual changes from baseline scores through Week 24 following treatment.

One of the study exploratory endpoints is aimed at determining feasibility of succeeding in performing successful IT administration of MSC-NTF cells and of blinding patients and caregivers to the treatment in anticipation of performing a larger Phase III efficacy study.

ALS is a terminal disease, and life expectancy of patients is usually 3 to 5 years after diagnosis of ALS. Early stage ALS patients (≤24 months from ALS symptom onset and ALSFRS-R ≥30) were therefore chosen as the study population, to increase chances of participants of completing the full 9 months study and to obtain a patient population with a relatively homogenous rate of disease progression thus increasing the power for detecting a difference in the efficacy outcomes (either between treated and controls or change from baseline among treated vs. untreated subjects). Rates of decline on the ALSFRS-R in such patients are reported in the published scientific literature to range from -0.92 ± 0.08 points/month (Castillo-Viguera et al 2010, NEALS data) to 2.35 (Sorenson EJ et al. 2008).

Since ALS is a fatal, progressive, neurodegenerative disease characterized by motor-neuron cell death in the brain and spinal cord, accompanied by rapid loss of muscle control and eventual complete paralysis and there is currently no available treatment to prevent its progressive course, a reduction in the slope of decline in the ALSFRS-R and/or in the SVC reflected as a change in disease progression (slope) compared to concurrent placebo controls will be considered to constitute a response that will be evaluated further in Phase III clinical studies.

6.4. SUBJECT POPULATION

This study will be conducted in subjects with a clinical diagnosis of ALS who meet the El Escorial criteria (Brooks, B.R., et al 2000) for possible, laboratory-supported probable, probable, or definite ALS. To be enrolled in this study, patients must meet all inclusion criteria in Section 6.4.1 below and must not have any of the exclusion criteria listed in Section 6.4.2.

The subject population is chosen from the group of early-stage ALS participants with the aim of obtaining a homogeneous study population that will facilitate the interpretation of the study results and allow for identifying trends in efficacy outcomes.

Due to the length of the study it is also aimed to include participants that will survive for the duration of the study.

6.4.1. Inclusion Criteria

Study subjects meeting all of the following criteria will be allowed to enroll in the study:

1. Males and females ages 18 to 75 years old, inclusive.

2. ALS diagnosed as possible, laboratory-supported probable, probable, or definite as defined by revised El Escorial criteria.
3. Disease onset, as defined by first reported occurrence of symptomatic weakness, spasticity, or bulbar symptoms, of more than 12 months and less than or equal to 24 months.
4. Current disease symptoms must include limb weakness.
5. ALSFRS-R ≥30 at the Screening Visit.
6. Upright slow vital capacity (SVC) measure ≥65% of predicted for gender, height, and age at the Screening Visit.
7. Subjects must be taking a stable dose of riluzole for at least 30 days prior to enrolment or not be on riluzole, and not have been on it for at least 30 days prior to enrolment (riluzole-naïve subjects are permitted in the study).
8. Capable of providing informed consent and willing and able to follow study procedures, including willingness to undergo lumbar puncture.
9. Geographic accessibility to the study site and willingness and ability to comply with follow-up.
10. Women of child-bearing potential must agree not to become pregnant for the duration of the study. Women must be willing to consistently use two forms of contraceptive therapy throughout the course of the trial, and undergo a pregnancy test one week before bone marrow aspiration. Men must be willing to consistently use two forms of contraceptive if their partners are of child-bearing age.
11. Citizen or permanent resident of the United States.

6.4.2. Exclusion Criteria

Study subjects meeting any of the following criteria during screening evaluations will be excluded from entry into the study:

1. Prior stem cell therapy of any kind.
2. Inability to lie flat for the duration of intrathecal cell transplantation and/or bone marrow biopsy, or inability to tolerate study procedures for any other reason.
3. History of autoimmune disease (excluding thyroid disease) myelodysplastic or myeloproliferative disorder, leukemia or lymphoma, whole body irradiation, hip fracture, or severe scoliosis.
4. Any unstable clinically significant medical condition other than ALS (e.g., within six months of baseline, had myocardial infarction, angina pectoris, and/or congestive heart failure), treatment with anticoagulants that, in the opinion of the investigator, would compromise the safety of patients.
5. Any history of malignancy including any malignancy affecting the central nervous system and melanoma, within the previous 5 years, with the exception of localized skin cancers (with no evidence of metastasis, significant invasion, or re-occurrence within three years of baseline).
6. Serum AST or ALT value >3.0 times the upper normal limit.

7. Serum creatinine value >2.0 times the upper normal limit.
8. Positive test for Hepatitis B, Hepatitis C, HIV.
9. Current use of immunosuppressant medication or use of such medication within 4 weeks of Screening visit (Visit 1).
10. Any history of acquired or inherited immune deficiency syndrome.
11. Exposure to any other experimental agent (off-label use or investigational) or participation in a clinical trial within 30 days prior to Screening Visit (Visit 1).
12. Use of non-invasive ventilation (NIV), diaphragm pacing system or invasive ventilation (tracheostomy).
13. Any history of either substance abuse within the past year, or unstable psychiatric disease according to PI judgment.
14. Placement or usage of feeding tube.
15. Pregnant women or women currently breastfeeding.

6.5. STUDY ASSESSMENTS

The Schedule of Activities (SOA) provides a visual listing of study activities at each visit.

Refer to Appendix 1 for table of SOA at each visit and the study manual for details of assessments, including the ALSFRS-R, SVC, HHD, EIM and C-SSRS.

This is a multi-center study. The Sponsor will ensure that all Medical centers will be performing study assessment procedures in the same way by providing appropriate training to sites.

6.5.1. Clinical Laboratory Safety Tests

Clinical laboratory safety tests will be monitored throughout the trial at Visits 1, 3, 5, 7, 8, 9 and 10 as listed in the Schedule of Activities (Tables 1 and 2).

Tests include:

Hematology: CBC (RBC with Indices, WBC with differential and platelet count, Hb, Ht).

Blood Biochemistry: Na, K, Cl, HCO3, BUN, Cr, Gluc, Ca, Mg, Phos, total protein, triglycerides (TG), Total cholesterol, HDL, LDL, urea, creatinine, total bilirubin, AST(GOT), ALT(GPT), ALP, uric acid.

Coagulation: PT, PTT.

Urinalysis (dip-stick test) - Specific Gravity, pH, glucose, protein, ketones, blood.

6.5.2. Physical Examinations, Vital Signs, and Electrocardiograms

Participants will undergo physical examinations at all in-person visits except for the Bone Marrow aspiration visit (Visit 4), Vital Signs measurements (including blood pressure, pulse and respiration rate after sitting for at least 3 minutes) as well as body weight will be monitored at all in-person visits, and a 12-lead ECG will be obtained at visits 1, 5 and 10.

6.5.3. Pre-transplantation Visits

6.5.3.1. Visit 1: Screening Visit

Visit 1 is the screening Visit and precedes V2 by approximately 4-6 weeks. Subjects will undergo the following screening assessments:

- Obtain Informed consent
- Collect demographic data
- Medical history
- History of ALS symptoms and date of diagnosis
- Review of concomitant medications
- Physical examination including height and weight
- El Escorial criteria
- Neurological examination
- Blood collection for hematology, coagulation, chemistry evaluations and a pregnancy test (Female participants)
- Blood collection for HBV (surface and core antigen), HCV, HIV 1 and 2 and HTLV I and II, Treponema pallidum, and CMV tests
- Urinalysis
- Electrocardiogram (ECG)
- Vital sign measurements
- SVC pulmonary function test
- ALSFRS-R questionnaire
- Hand held dynamometry (HHD)
- Electrical impedance myography (EIM) will be collected only at centers that opt to participate in EIM data collection.
- Columbia Suicide Severity Rating Scale (C-SSRS) Baseline
- Determine study eligibility

6.5.3.2. Visit 2: Pre transplantation (Week 4-6)

Visit 2 is the first visit of the pre transplantation follow-up period (Week 4-6). Participants will undergo the following assessments

- Review of concomitant medications
- Directed physical examination including weight
- Vital sign measurements
- Neurological examination
- SVC pulmonary function test
- Adverse events review
- ALSFRS-R questionnaire
- Hand held dynamometry (HHD)
- Electrical impedance myography (EIM) will be collected only at centers that opt to participate in EIM data collection.
- Columbia Suicide Severity Rating Scale (C-SSRS) Since Last Visit
- Confirm study eligibility

6.5.3.3. Visit 3: Pre transplantation Visit (Week 8-10)

Visit 3 is the second visit of the pre-transplantation follow-up period (Week 8-10), about 1 week before Bone Marrow aspiration. Participants will undergo the following assessments:

- Review of concomitant medications
- Directed physical examination including weight
- Vital sign measurements
- Neurological examination
- Blood collection for hematology, coagulation and chemistry evaluations and a pregnancy test (Female participants)
- Blood collection for HBV (surface and core antigen), HCV, HIV 1 and 2 and HTLV I and II, Treponema pallidum, and CMV tests.
- Urinalysis
- SVC pulmonary function test
- Review of adverse events
- ALSFRS-R questionnaire
- Hand held dynamometry (HHD)
- Electrical impedance myography (EIM) will be collected only at centers that opt to participate in EIM data collection.
- Columbia Suicide Severity Rating Scale (C-SSRS) Since Last Visit

Following Visit 3, participants will be randomized into two arms at a 3:1 ratio: the treatment transplant arm (36) and the placebo transplant arm (12).

Any participant discontinuing the study prior to transplantation of cells (or placebo) injections will be replaced with another participant to meet the target of 48 transplanted participants.

Participants and medical team will be blinded to patient randomization.

6.5.3.4. Visit 4: Bone Marrow Aspiration (Week 9-11)

Once all safety test results are confirmed negative or normal, all participants will undergo:

- Review of concomitant medications
- Review of adverse events
- Vital sign measurements

After these assessments, all participants will undergo bone marrow aspiration (BMA) by a credentialed health care provider as per Medical Centre procedures from multiple punctures of the iliac crest of the patients' pelvic bone.

6.5.3.5. Visit 5: Cell Transplantation (Days 0-2) 24-38 days from BMA

At the transplantation visit, subjects will be admitted to an inpatient study unit for study procedures. Pre-transplant activities will include:

- Review of concomitant medications
- Review of adverse events
- Vital sign measurements
- Directed physical examination including weight
- Neurological examination

- SVC pulmonary function test
- ALSFRS-R questionnaire
- Hand held dynamometry (HHD)
- Electrical impedance myography (EIM) will be collected only at centers that opt to participate in EIM data collection.
- Columbia Suicide Severity Rating Scale (C-SSRS) Since Last Visit

Following pre-transplant procedures, subjects will undergo intrathecal injection of cells or placebo as well as 24 intramuscular injections of cells or placebo (transplantation) along the biceps and triceps muscle of the right arm (If the physician is unable to inject into the right arm, the cells may be injected into the left arm and the fact recorded on the CRF. See Appendix 4, describing the procedure for the IM injections). CSF removed from the subject immediately prior to the intrathecal administration of cells will be retained for analysis.

Concomitant medications and adverse events will be monitored throughout the study visit, as necessary. In addition the following will be monitored:

- Vital signs will be monitored at hours 1, 2, 3, 4, 6, 16, 22, 28, 40, and upon discharge at 44 hours or up to 72 hours post transplantation. Inpatient observation is up to 72 hours, with earlier discharge at investigator discretion.
- Visual inspection of the injection sites will be performed at hours 1, 16 and 40.
- Directed physical examinations will be performed at hours 16, and 40 post-transplantation.
- Hematology, coagulation chemistry evaluations and biochemistries as well as urinalysis will be checked at 16 hours.
- Electrocardiogram (ECG) will be performed at 22 ± 4 hours post-transplantation

Prior to discharge, activities will include: vital signs, review of medications and adverse events and questionnaire for assessment of blinding.

6.5.4. Post transplantation follow-up

6.5.4.1. Visit 6: Week 2 (± 5 days) Follow-Up

At the week 2 post transplantation follow-up visit participants will undergo:

- Review of concomitant medications
- Review of adverse events
- Vital sign measurements
- Directed physical examination including weight
- Neurological examination
- ALSFRS-R questionnaire
- SVC pulmonary function test
- Hand held dynamometry (HHD)
- Lumbar puncture and collection of 3 mL of CSF.
- Electrical impedance myography (EIM) will be collected only at centers that opt to participate in EIM data collection.
- Columbia Suicide Severity Rating Scale (C-SSRS) Since Last Visit

6.5.4.2. Visit 7: Week 4 (± 5 days) Follow-Up

At the week 4 post transplantation follow-up visit participants will undergo:

- Review of concomitant medications
- Review of adverse events
- Vital sign measurements
- Directed physical examination including weight
- Blood collection for haematology coagulation and chemistry evaluations
- Urinalysis
- Neurological examination
- ALSFRS-R questionnaire
- SVC pulmonary function test
- Hand held dynamometry (HHD)
- Electrical impedance myography (EIM) will be collected only at centers that opt to participate in EIM data collection.
- Columbia Suicide Severity Rating Scale (C-SSRS) Since Last Visit

6.5.4.3. Visit 8: Week 8 (± 5 days) Follow-Up

At the week 8 post transplantation follow-up visit participants will undergo:

- Review of concomitant medications
- Review of adverse events
- Vital sign measurements
- Directed physical examination including weight
- Blood collection for haematology, coagulation and chemistry evaluations
- Urinalysis
- Neurological examination
- ALSFRS-R questionnaire
- SVC pulmonary function test
- Hand held dynamometry (HHD)
- Electrical impedance myography (EIM) will be collected only at centers that opt to participate in EIM data collection.
- Columbia Suicide Severity Rating Scale (C-SSRS) Since Last Visit

6.5.4.4. Phone Call 1: Week 12 (± 5 days) Follow-Up

Subjects will receive a phone call for this Week 12 follow-up.

During the phone interaction, subjects will undergo:

- Review of concomitant medications
- Review of adverse events
- ALSFRS-R questionnaire

6.5.4.5. Visit 9: Week 16 (± 5 days) Follow-Up

At the week 16 post transplantation follow-up visit participants will undergo:

- Review of concomitant medications
- Review of adverse events
- Vital sign measurements

- Directed physical examination including weight
- Neurological examination
- Blood collection for haematology, coagulation and chemistry evaluations
- Urinalysis
- ALSFRS-R questionnaire
- SVC pulmonary function test
- Hand held dynamometry (HHD)
- Electrical impedance myography (EIM) will be collected only at centers that opt to participate in EIM data collection.
- Columbia Suicide Severity Rating Scale (C-SSRS) Since Last Visit

6.5.4.6. Phone Call 2: Week 20 (± 5 days) Follow-Up

Subjects will receive a phone call for this Week 20 follow-up.

During the phone interaction, subjects will undergo:

- Review of concomitant medications
- Review of adverse events
- ALSFRS-R questionnaire

6.5.4.7. Visit 10: Week 24 (± 5 days) Follow-Up

At the week 24 post transplantation follow-up visit participants will undergo:

- Review of concomitant medications
- Review of adverse events
- Vital sign measurements
- Physical examination including weight
- Neurological examination
- Blood collection for haematology coagulation and chemistry evaluations
- Urinalysis
- Electrocardiogram (ECG)
- ALSFRS-R questionnaire
- SVC pulmonary function test
- Hand held dynamometry (HHD)
- Electrical impedance myography (EIM) will be collected only at centers that opt to participate in EIM data collection.
- Columbia Suicide Severity Rating Scale (C-SSRS) Since Last Visit
- Questionnaire for assessment of blinding

6.5.5. STUDY DISCONTINUATION

Subjects could choose to discontinue the study at any time, for any reason, specified or unspecified, and without prejudice. Participants could be discontinued from the study for any of the following reasons:

- Participants whose MSC fail to proliferate and to produce a sufficient amount of cells for transplantation (see section 6.3.1)
- At the participant's request
- At the discretion of the Investigator, if deemed appropriate, for any reason
- At the discretion of the Sponsor, if deemed appropriate, for any reason

In addition to the circumstances listed above for patients' withdrawal from the study, Brainstorm Cell Therapeutics Ltd. and the Investigators reserve the right to terminate the study at any time. In any case of early termination (ET) of the study, Brainstorm Cell Therapeutics Ltd. and the Investigators will ensure that adequate consideration is given to the protection of each subject's interest.

An ET visit will be conducted only for subjects who discontinue the study after treatment, post visit 5. The ET visit will include all the procedures required at end of study visit (Visit 10).

Any participant discontinuing the study prior to transplantation of cells (or placebo) injections will be replaced with another participant to meet the target of 48 transplanted participants.

6.5.6. Temporary Treatment Discontinuation

Since study treatment is only administered once during this trial, study treatment cannot be temporarily held for any serious adverse event or significant intercurrent illness.

6.5.7. Permanent Treatment Discontinuation

Permanent treatment discontinuation is defined as cessation of study drug administration. This may only occur if the subject does not receive all the intended doses of study treatment at the single treatment period (e.g., not all of the intended IM and/or IT doses are administered). Safety follow-up (Section 6.5.8.) will still be performed.

The primary reasons for permanent treatment discontinuation are listed in Section 6.8.4. Cross-references are provided to protocol sections with additional information.

Reason	Comment
Adverse event or intercurrent illness	Any intolerable adverse event that cannot be ameliorated by the use of adequate medical intervention or that in the opinion of the Investigator or Medical Monitor would lead to undue risk if study treatment were continued.
Sponsor discontinuation of study	The sponsor reserves the right to terminate the study anytime as described in Section 6.12.7. The sponsor will terminate this study following completion of the study objectives, or earlier if deemed necessary.
Participant decision	Participants may permanently discontinue study treatment anytime for any reason. Following study drug discontinuation, patients should have protocol-required safety follow-up assessments unless the patient specifically declines further follow-up.

6.5.8. Safety Follow-Up

All patients who are treated or partially treated will have safety follow-up approximately 9 months from enrolment in the study. Adverse events and serious adverse events will be followed up as described in Section 6.8. For patients who refuse further clinic study visits, telephone contact and/or home visits by study staff should be attempted and documented to review for adverse events.

6.5.9. Lost to Follow-Up

Every reasonable effort will be made to contact any patient apparently lost to follow-up during the course of the study to complete study-related assessments and record outstanding data.

Following unsuccessful telephone contact, an effort to contact the patient by mail using a method that provides proof of receipt will be attempted. Alternate contacts will be used if the patient is not reachable (eg, primary care providers, referring physician, relatives). Such efforts should be documented in the patient's source documents.
If all efforts fail to establish contact, the patient will be considered lost to follow-up.

6.6. INVESTIGATIONAL PRODUCT INFORMATION

6.6.1. General Information

The cell therapy is based on the autologous transplantation of adult bone marrow derived multipotent mesenchymal stromal cells (hMSC) which are induced *ex-vivo* to secrete neurotrophic factors (NTFs) such as Glial Cell Line Derived Neurotrophic Factor (GDNF), Brain-derived neurotrophic factor (BDNF), Vascular Endothelial Growth Factor and Hepatocyte Growth Factor (HGF) and are thus designated MSC-NTF cells. The MSC-NTF cells are derived from hMSCs isolated from the patient's own Bone Marrow, propagated *in-vitro* and induced to secrete NTFs using a medium based procedure.

MSC-NTF cells are adult stem cells that are used for autologous "Self-transplantation". There is no ethical or safety issues of involvement of embryonic cells. Since the cells are the patient's own cells there is no risk of rejection and no need for immunosuppressive agents, which can cause severe and/or long-term side effects.

MSC-NTF cells delivery is easy and safe by standard procedures (IT and IM injections) and does not require surgical intervention.

6.6.2. MSC-NTF Product Characteristics

Participants' bone marrow is aspirated and MSC are isolated from the total bone marrow mononuclear cell population, propagated in culture and induced to secrete NTFs. The MSC-NTF cells are then transplanted back into the patient as following:

- 125 x10^6 cells by IT administration (however, if less than 125 x 10^6 cells are available, then the total available dose of cells should be administered, provided at least 100 x 10^6 cells are administered)
- 48 x10^6 cells by IM administration.

Patients randomized to placebo will receive both IT and the same number of IM injections

The MSC-NTF cells' production process is carried out in the absence of antibiotics in the absence of phenol red and in the absence of animal derived components. The production process is cGMP compliant and is performed under full environmental control, in a class 10,000 cleanroom (ISO 7). All cell manipulation procedures are performed in a class 100 (ISO 5) laminar flow hood.

The MSC-NTF cells are provided in a ready-to-use participant-personalized unique treatment package with the appropriate primary and secondary labels. The treatment

package consists of one 5 ml syringe for IT transplantation, and twenty four 1 ml syringes for IM transplantation. Each treatment package consists of ready-for-injection syringes containing freshly harvested autologous cultured MSC-NTF cells at the dose defined for the appropriate route of administration in the clinical study protocol.

Syringes will be capped with a stopper (not a needle). The 5 ml syringe for IT transplantation will be packed in a pouch. The 1 ml syringes for IM transplantation will be placed in a 7-compartment tray that will be packed in a pouch.

The treatment/placebo package is delivered to the clinical site in a shipping system container designed for maintaining a temperature of 2-8°C during shipment. The shipping system containing the syringes is shipped via ground transportation to the clinical site. Product should be administered to the patient within 5 hours from packaging.

Placebo will be provided in the same number of syringes types and sizes as the cell-containing syringes.

All treatment as well as placebo syringes will be masked to preclude physician and patient's identification of their content. In addition the sponsor will make every effort to ensure blinding of the study by the attending physicians.

The cell production process, including the in-process controls is described in full detail in the CMC section and in the Investigator's brochure (IB).

6.6.3. Treatment Compliance

It is expected that participants will be fully compliant during the pre-transplant follow-up period.

Since patients are recruited at the early stage of the disease and ambulatory (Disease symptoms onset $\leq$ 24 months and ALSFRS-R $\geq$30 prior to Screening Visit) they are expected to be able to complete the full 6 months post treatment follow-up.

To increase chances of post–treatment compliance, it will be attempted to recruit patients living in the vicinity of the medical centers and/or previously known to the Investigators.

6.6.4. Test product, Dose and Administration

Placebo or participants' autologous MSC-NTF cells will be used for a combination treatment of 125x 10^6 cells intrathecally, (however, if less than 125 x 10^6 cells are available, then the total available dose of cells should be administered, provided at least 100 x 10^6 cells are administered), and 2x10^6 cells/site intramuscularly divided equally among 24 sites in the right biceps and triceps muscles unilaterally.

6.7. PRIOR AND CONCOMITANT THERAPY

6.7.1. Prior Therapy

Participants who received prior cell therapy of any kind will be excluded from the study (See Section 6.4.2).

Rilutek (riluzole) and Nuedexta (dextromethorphan hydrobromide and quinidine sulfate) are the only FDA-approved drugs for patients with ALS (Nuedexta is approved only to

treat pseudobulbar affect that occurs in some patients with ALS). Study participants must be on a stable dose of riluzole for at least 30 days prior to screening, or not on riluzole at all with no plans to begin therapy with riluzole for the duration of the study.

6.7.2. Concomitant Therapy

Concomitant medications given to the patient during the pre-transplant, in-patient post-transplant and outpatient post-transplant periods will be recorded.

Patients who were on a stable dose of riluzole for at least 30 days prior to screening will continue taking riluzole prior to study enrolment, unless requiring discontinuation for standard side-effects.

6.8. SAFETY REPORTING

For this study, AEs and SAEs will be collected from screening visit through the end of the study period and as detailed in Section 6.8.1.

6.8.1. Adverse Events definitions and reporting

Standard definitions for AEs are provided in this section for informational purposes.

6.8.1.1. Adverse Event (21 CFR 312.32(a))

AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality.

6.8.1.2. Serious Adverse Event (21 CFR 312.32(a))

An AE or suspected adverse reaction is considered "serious" (SAE) if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- Life-threatening (An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.)
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

If it is not certain that an event meets the above definitions of an SAE, the site investigators will contact the Medical Monitor to discuss.

6.8.1.3. Relatedness (Causality)

Investigators will assess relatedness of adverse events to study drug using the following terms:

- **Definite**: An AE that has a clear temporal association with investigational product administration (e.g., within 24 hours); provides a plausible pharmacologic explanation for the event;
- **Probable:** There is a reasonable temporal association with administration of the investigational product; unlikely caused by other drugs or underlying conditions;
- **Possible**: There is a plausible temporal association with the investigational product, but other etiologies are possible and relatedness to the investigational product cannot definitely be ruled out.
- **Unlikely:** The temporal association with the investigational product is implausible (but not impossible). The event is likely related to other drugs or conditions.
- **Not Related**: An AE with no temporal association with the investigational product but rather related to other etiologies such as concomitant medications or conditions or subject's known clinical state; subject has not received investigational product.

6.8.1.4. Severity (Intensity)

The severity of an adverse event will be graded on a scale: mild, moderate, severe, as defined below:

- **Mild**: Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated.
- **Moderate**: Minimal, local or non-invasive intervention indicated; interferes with age-appropriate activities of daily living.
- **Severe**: Disabling; unable to carry out age-appropriate activities of daily living.
- **Potentially Life-Threatening**: Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death

6.8.1.5. Follow-Up of AEs

After the initial recording of an AE, the Investigator should proactively follow the patient. Any non-serious AEs that are still on-going at the end of the study should be reviewed to determine if further follow-up is required. The Investigator will document on the eCRF any/all on-going non-serious AEs that will not be followed further after the patient exits the study. If in doubt, the Investigator should consult the study Medical Monitor.

All SAEs should be followed until resolution, until the condition stabilizes, or until the patient is lost to follow-up, or otherwise explained. Once the SAE is resolved, the corresponding AE eCRF page should be updated. Additionally, any relevant laboratory test reports, consultation reports from other health care professionals, discharge summaries, or other information that has been gathered about the event should be transmitted to the Sponsor.

The Sponsor may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of any AE.

6.8.1.6. Outcome

The following terms will be used during this study:

- Fatal
- Not Recovered/resolved
- Recovering/resolving
- Recovered/resolved
- Recovered/resolved with sequelae
- Unknown

6.8.1.7. Clinically Significant Laboratory Abnormalities

Any laboratory abnormalities deemed clinically significant by the Investigator should be reported on the AE CRF. A clinically significant abnormality is a confirmed abnormality (by repeat test) that is changed sufficiently from Screening so that in the judgment of the Investigator a change in management is warranted. This alteration may include: monitoring the laboratory test further, initiating other diagnostic tests or procedures, changing ongoing treatment, or administering new treatment. Whenever possible, the etiology of the abnormal finding (e.g., anemia) will be recorded on the CRF. Repeated additional tests and/or other evaluations required to establish the significance and etiology of an abnormal result should be obtained when clinically indicated.

6.8.2. Reporting Responsibilities and Procedures for AEs and SAEs

It is the responsibility of the Investigator or Sub-Investigator(s) to perform periodic assessment of all AEs/SAEs.

A subject, who experiences an AE, whether serious or not serious, should receive appropriate treatment and medical supervision as clinically indicated. AEs/SAEs will be followed throughout the subject's participation in the study, until resolution/stabilization or until a time that is mutually agreed upon between the Medical Monitor and the Investigator.

The Investigator must report to the Sponsor all SAEs within 24 hours of learning about the event. The reporting mechanism for an SAE is by submitting all available information about the event via fax to the designated Safety Department contact. If the SAE has not resolved at the time the Investigator submits an initial SAE report, the Investigator must provide a follow-up report as soon as the event resolves (or upon receipt of significant information if the event is still ongoing).

The following information and assessments will be recorded in the adverse event section of the SAE Reporting Form:

- The date and time of onset of the event and when it ended using the 24 hour clock where midnight is 00:00 and noon is 12:00.
- The signs, symptoms, or diagnosis of the event.
- The adverse event severity using the criteria outlined above.
- The relationship of the event to the investigational product as outlined above.

- The seriousness of the event according to definitions outlined above.
- A description of any required therapy, medication, treatment, or diagnostic procedure.
- Clinical data prior to the event, such as nutrition, concomitant medications, physical activity, etc.
- Any additional data which might be relevant to the event.

A written report is also required for all patients who died during the study. This report must document the events surrounding the patient's death and the cause of death. Attach a copy or summary of autopsy findings, if performed.

All SAE reports and questions pertaining to an SAE should be directed to:

1) **Drug Safety:** Katherine Smith, MD
Office: (919) 262-5626
Email: saereports@drugsafety.biz
Fax: (919) 844-69482)

2) Medical Monitor: Kenneth J. Tack, MD
Office: (810) 227-1386
Email: kjtack@comcast.net
Cell: (810) 355-8218

3) Sponsor: Tony Fiorino MD, Ph.D.
Office: (201) 357-5382
Email: tfiorino@brainstorm-cell.com

Yael Gothelf Ph.D.
Office: (646) 666-3188 Ext. 103
Email: ygothelf@brainstorm-cell.com

Brainstorm Cell Therapeutics Ltd.
12 Bazel St.
Kiryat Aryeh Petach Tikva
49001 ISRAEL

The Sponsor or designated CRO will report Investigational New Drug (IND) Safety Reports to the FDA and Investigators in accordance with the FDA regulations detailed in the Code of Federal Regulations (CFR) 21CFR312.32 and in accordance with Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies, December 2012. The Investigator at each study site is responsible for reporting SAEs to his or her Institutional Review Board (IRB) in accordance with local IRB procedures.

If new sites are added to the study, the Sponsor or designated CRO will notify all investigators at the sites involved in the study in writing of any severe/serious or

unexpected adverse events when this information is of global importance to subject safety and welfare.

6.8.3. Prospective assessment of the occurrence of suicidality

There is no evidence from animal or previous human studies to suggest that MSC-NTF cell transplantation will increase suicidal ideation or attempts; but, because these cells are delivered to the CSF and are active in the central nervous system, we plan to monitor suicidal ideation and behavior carefully throughout the trial.

Suicidal ideation and behavior will be monitored using the Columbia Suicide Severity Rating Scale (C-SSRS; http://www.cssrs.columbia.edu), delivered at each in-person trial visit. All study staff delivering the C-SSRS will be fully trained in its appropriate use and only study staff prepared to appropriately respond to subjects exhibiting suicidal ideation or behavior will deliver the scale. The 'Baseline' questionnaire will be given at the Screening/Visit. The 'Since Last Visit' questionnaire will be given at subsequent visits.

6.8.4. STUDY DISCONTINUATION

6.8.4.1. Study or Site Termination

Conditions may arise during the study that could prompt the study to be halted or the study site to be terminated. Conditions that may prompt such considerations include, but are not limited to, the following:

1. The discovery of unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
2. A decision on the part of the Data and Safety Monitoring Board (DSMB) to suspend or discontinue the study.
3. A decision on the part of Sponsor to suspend, discontinue, or shorten the study.
4. Study conduct at the study site may warrant termination under conditions that include the following:
    a) Failure of Investigator(s) to enrol eligible subjects into the study;
    b) Failure of Investigator(s) to comply with ICH-GCP guidelines, or FDA guidelines and regulations;
    c) Submission of false information from the research facility to the Sponsor, the Clinical Monitor, the FDA, or IRB;
    d) Insufficient adherence to protocol requirements;
    e) A conflict of interest of the Investigator, his/her institution, or site personnel that would negatively impact the integrity of the clinical trial;
    f) Institution or IRB under investigation for cause by a regulatory agency.

6.8.4.2. Subject Withdrawal from Study

Subjects may voluntarily withdraw from the study at any time during the course of the study.

The Investigator will document on the appropriate CRF page the reason/circumstances for withdrawal.

Efforts will be made to follow all subjects who discontinue study for any reason. Such follow up will include all relevant evaluations for safety including clinical assessments and collection of laboratory study results as set out in this protocol.

6.8.4.3. Study stopping rules

Previous clinical studies with MSC-NTF cells did not result in any treatment-related SAEs. However, if in the course of this study, 2 or more subjects experience SAEs evaluated as possible, probable or definitely related to product administration, patient enrolment and dosing will be temporarily suspended pending DSMB review of the subjects with SAEs.

6.8.5. Clinical Laboratory Safety Tests

Clinical laboratory safety tests will be monitored throughout the trial at Visits 1, 3, 5, 7, 8, 9 and 10 as listed in the Schedule of Activities (Tables 1 and 2).

All samples to be tested will be shipped to a Central Laboratory.

Tests include:

Hematology: CBC (RBC with Indices, WBC with differential and platelet count, Hb, Ht)

Coagulation: PT, PTT

Blood Biochemistry: Na, K, Cl, HCO3, BUN, Cr, Gluc, Ca, Mg, Phos, total protein, triglycerides (TG), Total cholesterol, HDL, LDL, urea, creatinine, total bilirubin, AST(GOT), ALT(GPT), ALP, uric acid.

Urinalysis (dip-stick test) - Specific Gravity, pH, glucose, protein, ketones, blood

6.8.6. Physical Examinations, Vital Signs, and Electrocardiograms

Participants will undergo physical examinations at all in-person visits except at the Bone Marrow Aspiration (BMA) visit (Visit 4), Vital Signs measurements (including blood pressure, pulse and respiration rate after sitting for at least 3 minutes) as well as body weight will be monitored at all in-person visits, and a 12-lead ECG will be obtained at visits 1, 5 and 10.

6.9. ASSESSMENT OF ENDPOINTS

6.9.1. Primary Endpoint:

6.9.1.1. Safety

The primary endpoint of the trial is the safety of MSC-NTF transplantation by IT and IM routes in participants with ALS

Safety will be assessed based on the incidence of treatment-emergent adverse events (TEAEs) (including serious adverse events [SAEs]) including clinically relevant changes in vital signs, clinical laboratory assessments, physical and neurological examinations, and electrocardiogram (ECG) tests.

6.9.2. Secondary Endpoints:

6.9.2.1. Revised ALS Functional Rating Scale (ALSFRS-R)

The ALSFRS-R is a quickly administered (10 minutes) ordinal, validated rating scale (ratings 0-4) used to determine patients' assessment of their capability and independence in 12 functional activities. All 12 activities are relevant in ALS. Initial validity was established by documenting that in ALS patients, change in ALSFRS-R scores correlated with change in strength over time, as measured by quantitative neuromuscular strength testing, and with quality of life measures, and predicted survival (Cedarbaum, J.M., et al. 1999, Greenberg, S.A., et al 2005). The test-retest reliability is greater than 0.88 for all test items. The advantages of the ALSFRS-R are that the categories are relevant to ALS, it is a sensitive and reliable tool for assessing activities of daily living function in patients with ALS, it is quickly administered, and is validated over the phone as well[1].

6.9.2.2. Slow Vital Capacity (SVC)

SVC measure the maximum amount of air a patient can exhale in a single breath. SVC is used frequently in ALS clinic as part of a battery of tests used to assess diaphragmatic weakness and monitor disease progression. SVC will be measured with patient seated in upright position. It can be measured quickly and effectively in the office setting.

6.9.3. Exploratory

6.9.3.1. Hand Held Dynamometry (HHD)

HHD is a quantitative measure of muscle strength and has been validated against maximum voluntary isometric contraction (MVIC) (Greenberg, S.A., et al. 2002). Proximal arm and distal arm muscles will be examined bilaterally. To normalize for varying strength of individual muscles, all values will be expressed as percent change from baseline; this value can be averaged to provide upper extremity, lower extremity, and total megascores. An additional analysis will use mean and standard deviation for each muscle group established from the initial values for each subject in this trial, so that strength determinations can be converted to Z scores (the difference between the obtained score and the mean, divided by the standard deviation). These Z scores can be combined in similar fashion to what was discussed above to produce megascores as well.

Muscle strength measurements (elbow flexion, wrist extension, knee extension, and ankle dorsiflexion) will be performed using the Hand Held Dynamometer (HHD), as described in appendix 2 at Visits 1,2,3,5,6,7,8, 9 and 10. The tests take approximately 20 minutes to complete.

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[1] Kasarskis EJ, Dempsey-Hall L, Thompson MM, Luu LC, Mendiondo M, Kryscio R. Rating the severity of ALS by caregivers over the telephone using the ALSFRS-R. Amyotroph Lateral Scler Other Motor Neuron Disord. 2005 Mar;6(1):50-4.;

Mannino M, Cellura E, Grimaldi G, Volanti P, Piccoli F, La Bella V. Telephone follow-up for patients with amyotrophic lateral sclerosis. Eur J Neurol. 2007 Jan;14(1):79-84.

6.9.3.2. Electrical Impedance Myography (EIM, Optional)

EIM measures the electrical impedance of individual muscles as a representation for muscle composition, which changes with disease progression. Using a single probe that contains both stimulating and recording electrodes, measurements are taken twice over each muscle. The probe is placed against a clean area of skin for less than 10 seconds per recording. Four muscles will be tested in upper and lower extremities; elbow flexors, wrist extensors, knee extensors, and ankle dorsiflexors, for a total of 8 muscles tested per subject. The minute electrical signals produced by the stimulator are imperceptible; subjects only notice the pressure of the probe against their skin. Sites will have the option of collecting the EIM outcome data.

6.9.3.3. Analysis of Cerebrospinal Fluid

Few studies have been performed that assess and quantify the presence of neurotrophic factors in the CSF. Since MSC-NTF secrete several known neurotrophic factors, we intend to develop ELISA assays for neurotrophic factors and use these assays to assess the concentration of these factors after treatment. We are also exploring the possible assessment of several putative ALS biomarkers in these CSF samples.

6.9.4. Statistical Methods and Sample Size Determination

Summaries for continuous variables will include the sample size, mean, standard deviation, median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means, standard deviations, and medians will be presented to one additional decimal place than reported in the raw values. Summaries for discrete variables will include frequencies and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%). Differences between treatment groups will be calculated as MSC-NTF cells – placebo and change from baseline will be calculated as post-treatment – pre-treatment (OR follow-up visit – baseline: e.g. Week 2 – baseline, Week 4 – baseline). The baseline visit will be defined as the last non-missing measure prior to initiation of investigational treatment. Additionally, for the pre-transplantation period and transplantation visits, change from screening (V1) summaries will be calculated as pre-transplantation period/transplantation visit – screening.

All efficacy analyses will use one-sided alpha = 0.10 tests and present one-sided 90% lower confidence limits and two-sided 95% confidence intervals around the difference between treatments as well as two-sided 95% confidence intervals around the point estimates within each treatment group. All summaries will be presented by treatment group.

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock, unblinding and analysis of study results.

6.9.4.1. Analysis Population

The safety population includes all randomized subjects who receive study treatment (treatment or placebo) including those who do not complete the study. The safety population will be analyzed as treated and will be used for the safety analysis.

The full analysis set (FAS) population includes all randomized subjects. The FAS will be analyzed as randomized. Analyses on the FAS population will be considered secondary.

The modified FAS (mFAS) population includes all FAS participants who receive study treatment. The mFAS will be analyzed as randomized. Analyses on the mFAS population will be considered primary.

The per protocol (PP) data set will include all mFAS subjects who have no major protocol violations likely to seriously affect the primary outcome of the study as judged by a blinded evaluation performed by a group of study personnel including the medical monitor, statistician, and clinical project manager prior to the unblinding of the study treatment. Analyses on the PP data set will group subjects according to the treatment actually received. Analyses on the PP population will be considered secondary.

Partially treated subjects will be included in the intention to treat analyses but won't be included in the per protocol analyses.

6.9.4.2. Safety analyses

Primary Objective: The safety of MSC-NTF transplantation via combined IT and IM injection in participants with ALS is the primary objective of this study. Safety endpoints include AEs, changes in physical and neurological examination findings, hematology, serum chemistry, urinalysis, vital signs, and requirement of concomitant medications.

All AEs will be coded to System Organ Class (SOC) and Preferred Term (PT) using the MedDRA®. The number of Treatment-Emergent Adverse Events (TEAEs) and the number of subjects with any TEAEs (along with percentages) will be tabulated by SOC and PT within each SOC by treatment group and over treatment groups. To count the number of subjects with any TEAEs, a subject who experiences multiple TEAEs within the same SOC will be counted only once for that SOC (whether or not the TEAEs are coded to the same PT). A subject who experiences multiple TEAEs coded to the same PT within the same SOC will be counted only once for that particular PT. In the summary, SOC will be listed in ascending alphabetical order; PTs will be listed in order of descending frequency for all subjects within each SOC.

Separate summaries will be provided for the following categories of AEs:

- TEAEs
- TEAEs by severity
- Treatment-related TEAEs
- Serious TEAEs

The proportion of subjects having each AE will be compared between treatment using Fisher's exact tests.

When evaluating changes in safety parameters, baseline will be defined as the last measurement prior to transplantation (i.e., prior to treatment).

Physical examination, neurological examination, hematology, serum chemistry, vital signs and concomitant medications will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) if the data is continuous and using counts and percentages if the data is discrete. Shifts from baseline in categorization of results (e.g. normal/abnormal or low/normal/high) will also be summarized.

6.9.4.3. Efficacy Analyses

Secondary Objectives: The change in slope between the treatment and placebo group and from pre-transplantation to post-transplantation in ALSFRS-R and in SVC (as a percent of normal for age and sex) will be estimated using the mixed linear statistical model.

The fixed effect variables in the model will be:

- Visit, expressed in days from the beginning of treatment (i.e. pre-treatment times will have negative values, post-treatment times positive values).
- Treatment
- Two-way interactions between visit & post-treatment indicator, (0 for pre-treatment visits, 1 for post-treatment visits) and visit & treatment
- Three-way interaction between visit & post-treatment visit indicator & treatment
- Site

The repeated measures within a subject over visit will also be accounted for in the model, wherein, the covariance structure will be evaluated using Bayesian information criterion (BIC). Covariance structures to be evaluated are: unstructured, toeplitz, spatial power with day, and compound symmetry.

The three-way interaction between visit & post-treatment visit indicator & treatment will be used to compare the change in slope in the treatment group to the change in slope in the placebo group.

The post-pre slope estimate within each treatment group will be used to test the change from pre-transplantation to post-transplantation.

Repeated measures covariance will be estimated by restricted maximum likelihood. The Kenward and Roger method will be used to determine degrees of freedom and compute p-values.

Secondary objectives will be evaluated for the FAS, as well as the PP populations.

Exploratory Objectives: The analysis for EIM (optional) and HHD will employ the same modeling approach as described above for the secondary objectives. The analysis for HHD will be based on a combined score reflecting muscles in the right arm.

A further analysis of HHD will compare the score for the right arm to the score for the left arm. The linear mixed model will include, in addition to the terms described above, an indicator for "right arm", interactions between that indicator and all other variables in the model, and a random effect term for the right arm indicator. Therefore, the fixed effect variables in the model will be:

- Visit, expressed in days from the beginning of treatment (i.e. pre-treatment times will have negative values, post-treatment times positive values);
- Treatment;
- Right arm indicator;
- Two-way interactions between visit & post-treatment indicator (0 for pre-treatment visits, 1 for post-treatment visits), visit & treatment, visit & right arm indicator, and treatment & right arm indicator;
- Three-way interactions between visit & post-treatment visit indicator & treatment, visit & post-treatment indicator & right arm indicator, and visit & treatment & right arm indicator;
- Four-way interaction between visit & post-treatment visit indicator & treatment & right arm indicator;

- Site.

6.9.4.4. Determination of sample size

No formal sample size calculation has been performed. The sample size chosen was not based on statistical considerations. The total of 36 treatment and 12 placebo subjects are expected to be a sufficient number to obtain adequate characterization of common TEAEs and to observe trends for treatment effects on the efficacy measures chosen for this study.

6.10. STUDY COMMITTEES AND COMMUNICATIONS

6.10.1. Data and Safety Monitoring Committee

An independent, three member Data Safety and Monitoring Board (DSMB) will be assembled for this Phase 2 clinical trial. The DSMB will consist of two expert neurologists (with ALS experience and no other involvement in this trial), with experience in safety trials and a statistician. The DSMB will review initial safety data after approximately 12 patients have been treated and at periodic intervals thereafter.

6.11. LABORATORY REQUIREMENTS

A central laboratory will analyze the clinical laboratory safety samples (hematology, serum chemistry) as described in Section 6.8.5 for this study. Laboratory samples will be sent to an independent laboratory for processing and analysis as specified by the Sponsor.

6.12. INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

6.12.1. Ethics

The Sponsor/Investigator will obtain, from the clinical sites Institutional Review Boards (IRB), prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the Sponsor/Investigator will promptly notify the clinical sites IRB of the deviation.

The clinical sites IRB operate in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (CGP).

In the event that the clinical sites IRB require, as a condition of approval, substantial changes to a clinical protocol submitted under an FDA-accepted IND application, or in the event of the Sponsor-Investigator's decision to modify the previously accepted clinical protocol the Sponsor/Investigator will submit (i.e., in advance of implementing the change) a Protocol Amendment to the IND describing any change to the Phase 2 protocol

that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study.

Examples of Phase 2 clinical protocol changes requiring the submission of a Protocol Amendment include:

- Any significant change in the number of subjects under study.
- Any significant change in the design of the protocol (such as the addition or deletion of a control group).
- The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor the safety of the investigational drug.

6.12.2. Data Quality Assurance

6.12.2.1. Data Management

Data from the study will be entered into CRFs in a validated database. Data review, coding, and logic, range, cross-form, and consistency checks will be performed to ensure quality of the data. Adverse events and medications will be coded using MedDRA and the World Health Organization Drug Dictionary (WHO-DD), respectively.

6.12.2.2. Case Report Forms

The study will use an electronic data capture system. All case report forms will be designed and provided to the site by the Sponsor or designee. All personnel accessing the electronic data capture system will be trained on the use of the system by the CRO responsible for data management. All case report form books are to be filled out completely, reviewed, and signed by the Investigator or sub-investigators listed on the Form FDA 1572.

6.12.2.3. Study Monitoring

The Sponsor or designee will monitor this study in accordance with current GCP guidelines. By signing this protocol, the Investigator grants permission to the Sponsor or designee and appropriate regulatory authorities to conduct onsite monitoring of all appropriate study documentation. To ensure the accuracy of data collected on the case report forms, it is mandatory that Sponsor representatives (e.g. study monitor) have direct access to original source documents (e.g. paper or electronic patient records, patient charts, and laboratory reports) needed to verify the entries on case report forms. During the review of these documents, the anonymity of the patient will be respected with strict adherence to professional standards of confidentiality.

A study monitor will contact and visit the site regularly and will be allowed, on request at a mutually acceptable time, to inspect the various original medical records (paper or electronic) related to the study. The study monitor will be responsible for inspecting the case report forms at regular intervals throughout the study, to verify the adherence to the protocol, and the completeness and correctness of all case report form entries. The Investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

6.12.2.4. Study Audits

During the course of the study and after study completion, it is possible that one or more quality assurance audits will be undertaken by authorized Sponsor representatives. The purpose of the audit is to ensure that the study is (or was) conducted and monitored in compliance with the protocol as well as recognized GCP guidelines and regulations. If such audits are to occur, they will be arranged for a reasonable and agreed upon time. By signing this protocol, the Investigator grants permission to the Sponsor or designee to conduct onsite audits of all appropriate facilities and study documentation.

6.12.3. Investigational Product Accountability

MSC-NTF cells are autologous cells prepared on a per-patient basis.

At the end of the production process the patient's MSC-NTF cells are loaded in the syringes and immediately shipped to the medical center for transplantation. MSC-NTF cells have been shown to be stable in the syringes for over 5 hours at 2-8°C.

Any syringes not administered to the patient will be immediately discarded as biohazard waste.

The manufacturing facility will be responsible for maintaining production records. The site will record the number of syringes administered to each patient.

6.12.4. Compensation, Insurance, and Indemnity

The subject will be appropriately treated or compensated, or both, for any health or other problems arising from participation in this study. In the event of a side effect or injury, appropriate medical care as determined by the Investigator or designated alternate will be provided.

If bodily injury is sustained, resulting directly from the use of the study drug or by required study procedures, the Sponsor will reimburse for reasonable physician fees and medical expenses necessary for treatment of only the bodily injury that is not covered by the patient’s medical or hospital insurance, provided that the injury is not due to a negligent or wrongful act or omission by the study doctor and study staff. No other compensation of any type will be provided by the Sponsor. Financial compensation for lost wages, disability, or discomfort due to the study participation or procedures is not available.

6.12.5. Data recording/Case Report Forms

Case Report Forms (CRFs,) will be completed for each subject enrolled into the clinical study. The Investigator will review, approve and sign/date each completed CRF; the Investigator’s signature serving as attestation of the Investigator’s responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic.

Source Data are the clinical findings and observations, laboratory and test data, and other information contained in Source Documents. Source Documents are the original records (and certified copies of original records); including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-

rays, etc. When applicable, information recorded on the CRF shall match the Source Data recorded on the Source Documents.

Any clinical study data that will be recorded directly on the CRF, whereupon the CRF data is to be considered the Source Data will be identified.

Subject names will not be supplied to the Sponsor. Only the subject number and subject initials will be recorded in the CRF. Subject names appearing on any other document (eg, laboratory report) must be redacted on the copy of the document to be supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of the Sponsor, IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. Electronic systems will be used as the sole instrument for the recording and analysis of clinical and laboratory data related to the safety and/or effectiveness of the study drug(s).

6.12.6. Record maintenance and retention

The Sponsor/Investigator will maintain records in accordance with Good Clinical Practice guidelines; to include:

- FDA correspondence related to the IND and clinical protocol, including copies of submitted Safety Reports and Annual Reports;
- IRB correspondence (including approval notifications) related to the clinical protocol; including copies of adverse event reports and annual or interim reports;
- Current and past versions of the IRB-approved clinical protocol and corresponding IRB-approved consent form(s) and, if applicable, subject recruitment advertisements;
- Signed FDA Form 1572 Statements of Investigator (i.e., for the Sponsor-Investigator) ;
- Financial disclosure information (i.e., for the Sponsor-Investigator and for sub-investigators who will be involved in the administration of the study drugs and/or the evaluation of research subjects [i.e., who will contribute significantly to the research study data]);
- Curriculum vitae (i.e., for the Investigator and for sub-investigator(s));
- Certificates of required training; e.g., human subject protections, Good Clinical Practice, etc. (i.e., for the Sponsor-Investigator and for all sub-investigators who will be involved in the administration of the study drugs and/or the evaluation of research subjects [i.e., who will contribute significantly to the study data]);
- Listing of printed names/signatures. (i.e., for the Sponsor-Investigator and for all sub-investigators who will be involved in the administration of the study drugs and/or the evaluation of research subjects [i.e., who will contribute significantly to the study data]);
- Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol;
- Laboratory certification information;
- Instructions for on-site preparation and handling of the investigational drug(s), study treatment(s), and other study-related materials (i.e., if not addressed in the clinical protocol);
- Responsibility delegation log;

- Signed informed consent forms;
- Completed Case Report Forms; signed and dated by Sponsor/Investigator;
- Source Documents or certified copies of Source Documents;
- Monitoring visit reports;
- Copies of Sponsor-Investigator correspondence (including notifications of safety information) to sub-investigators;
- Subject screening and enrolment logs;
- Subject identification code list;
- Investigational drug accountability records, including documentation of drug disposal;
- Final clinical study report;
- Decoding procedures for blinded trials;
- Master randomization list;
- Retained biological specimen log;
- Interim data analysis report(s).

The Investigator will retain the specified records and reports for up to 2 years after the marketing application is approved for the investigational drug; or, if a marketing application is not submitted or approved for the investigational drug, until 2 years after investigations under the IND have been discontinued and the FDA so notified.

6.12.7. Study Termination

The Sponsor will terminate this study following completion of the study objectives, or earlier if deemed necessary.

The Sponsor reserves the right to terminate the study at any time. When the Sponsor is aware of information on matters concerning the quality, efficacy, and safety of the study drug, as well as other important information that may affect proper conduct of the clinical study, the Sponsor may terminate the study and send a written notice of the termination along with the reasons to the Investigator.

If an Investigator intends to terminate participation in the study, the Investigator must immediately inform the Sponsor and provide the reason for it.

6.13. USE OF STUDY INFORMATION AND PUBLICATION

All information obtained during the conduct of the study will be considered to be confidential. Written permission from the Sponsor is required before disclosing any information relative to this study. All publications (e.g., manuscripts, abstracts, and slide presentations) based on this study must be submitted to the Sponsor for corporate review and release at least 30 days before submission.

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6.15. APPENDICES

6.15.1. Appendix 1: Listing of study activities

6.15.1.1. Scheduled monitoring events

Table 1: Schedule of Activities:

Study Period	**Screening**	**Pre-transplantation period**			**Cells/Placebo Transplantation Visit**	**Post-transplantation follow-up**						
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**Phone Call 1**	**V9**	**Phone Call 2**	**V10 EOS**
Procedure	**Screening**	**Enrolment**		**BMA**	**Transplantation**							
Time Schedule	**Precedes V2 by 4-6 wks**	**Wk 4-6**	**Wk 8-10**	**Wk 9-11**	**D0-2**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**
Informed consent	x											
Eligibility criteria	x	x										
Demographic data	x											
Height	x											
Body weight	x	x	x	x	x	x	x	x		x		x
Physical examination	x	x	x		x	x	x	x		x		x
12 lead ECG	x				x							x
Vital signs[1]	x	x	x	x	x	x	x	x		x		x
Medical History	x											
ALS Medical History	x											
El Escorial Criteria	x											
ALSFRS-R	x	x	x		x	x	x	x	x	x	x	x
Neurological Examination	x	x	x		x	x	x	x		x		x
EIM (Optional)	x	x	x		x	x	x	x		x		x
Slow Vital Capacity (SVC)	x	x	x		x	x	x	x		x		x
Muscle strength evaluation (MVIC - HHD)	x	x	x		x	x	x	x		x		x
Concomitant medication review	x	x	x	x	x	x	x	x	x	x	x	x
HIV 1 and 2	x		x									

Study Period	**Screening**	**Pre-transplantation period**			**Cells/Placebo Transplantation Visit**	**Post-transplantation follow-up**						
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**Phone Call 1**	**V9**	**Phone Call 2**	**V10 EOS**
Procedure	**Screening**	**Enrolment**		**BMA**	**Transplantation**							
Time Schedule	**Precedes V2 by 4-6 wks**	**Wk 4-6**	**Wk 8-10**	**Wk 9-11**	**D0-2**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**
HBV	x		x									
HCV	x		x									
HTLV I and II	x		x									
Treponema pallidum	x		x									
CMV	x		x									
Pregnancy test	x		x									
Hematology[2]	x		x		x		x	x		x		x
Blood biochemistry [3]	x		x		x		x	x		x		x
Coagulation tests [4]	x		x		x		x	x		x		x
Urinalysis [5]	x		x		x		x	x		x		x
Bone marrow aspiration				x								
Cell Transplant IM / IT					x							
CSF collection					x	x						
Visual inspection of injection site					x							
Adverse events review		x	x	x	x	x	x	x	x	x	x	x
Prospective assessment of the occurrence of suicidality	x	x	x		x	x	x	x		x		x
Assessment of blinding (Patient and Investigator)					x							x

BMA- Bone Marrow aspiration

Table 2: Detailed Schedule of Activities for Cell Transplantation Visit (V5):

Estimated Time	**08:00-16:00**	**16:00**	**17:00**	**18:00**	**19:00**	**20:00**	**22:00**	**8:00**	**14:00**	**20:00**	**8:00**	**12:00**
Time\ Procedure	**Up to 8 hours before transplant**	**Hr 0**	**Hr 1**	**Hr 2**	**Hr 3**	**Hr 4**	**Hr 6**	**Hr 16**	**Hr 22**	**Hr 28**	**Hr 40**	**Hr 44-72**
Admit to Inpatient Ward	x											
Body weight	x											
Physical Examination	x							x[1]			x[1]	
Vital signs[2]	x		x	x	x	x	x	x	x	x	x	x
12 lead ECG									x[8]			
ALSFRS-R	x											
Neurological Examination	x											
EIM (Optional)	x											
Slow Vital Capacity (SVC)	x											
Muscle strength evaluation (MVIC - HHD)	x											
Concomitant medication review[3]	x		x	x	x	x	x	x	x	x	x	x
Hematology[4]								x				
Blood biochemistry[5]								x				
Urinalysis[6]								x				
Coagulation[7]								x				
Cell Transplant IM / IT [1]		x										
Retention of CSF sample		x										
Visual inspection of injection site			x					x[1]			x[1]	
Adverse events review [3]	x		x	x	x	x	x	x	x	x	x	x
Prospective assessment of the occurrence of suicidality	x											
Assessment of blinding (Patient and Investigator)												x[8]
Discharge from Inpatient Setting												x

1 Time Window: +/- 1 hour

2 HR, BP, RR, Body temperature - Time Window: +/- 30 minutes

3 Ongoing data collection throughout visit as necessary

4 Hematology: CBC (RBC with Indices, WBC with differential and platelet count, Hb, Ht) - Time Window: +/- 2 hours

5 Blood Biochemistry: Na, K, Cl, HCO3, BUN, Cr, Gluc, Ca, Mg, Phos, total protein, triglycerides (TG), Total cholesterol, HDL, LDL, urea, creatinine, total bilirubin, AST(GOT), ALT(GPT), ALP, uric acid - Time Window: +/- 2 hours

6 Urinalysis (dip-stick test) - Specific Gravity, pH, glucose, protein, ketones, blood

7 Coagulation: PT, PTT

8 Can be done prior to discharge

6.15.2. Appendix 2: Muscle Strength using Hand Held Dynamometry

Muscle strength tests will be assessed at visits 1, 2, 3, 5, 6, 7, 8, 9 and 10

The evaluators will use the *MIRCOFET 2* HHD for all subjects in this study. The dynamometer will be zeroed prior to each muscle test by pressing the reset button. All subjects will be seated upright in a hardback chair with armrests for testing. If the subject cannot transfer to a chair then the subject can be tested in their wheelchair.

Each muscle will be tested twice and both of the values recorded. However, up to three trials can be performed if the variability between the first two trials is greater than 15 % or if the evaluator thinks that one of the first two trials was not valid. The numbers will be recorded on the forms provided by the coordination center.

The testing pad for the HHD should be changed to fit the contour of the subject's body. The finger test pad must be used for testing the first dorsal interosseous. The HHD should always be flat against the body part being tested and the force directed opposite to the direction of movement. Prior to testing the subject with the HHD, the evaluator must ensure that the subject is able to actively move into the test position.

The subject should rest between trials and then return to the starting position. The subject should be encouraged to push against the HHD with all of his/ her strength. Subject must hold maximal contraction for at least two seconds. Evaluator should match subject's resistance for at least two seconds before increasing their force to break the contraction. Encouragement needs to be consistent with all subjects.

Shoes and orthotics should be removed prior to testing the legs. Stabilization of the subject is very important and should follow the instructions provided for each muscle group. The subjects cannot hold on to the armrest during testing. Subjects can be supported with pillows or by another person if they have trunk instability. Subjects can use BIPAP if needed during the testing.

6.15.2.1. Shoulder Flexion

The subject is seated in a hard back chair with the shoulder flexed at 45 degrees to the angle of the trunk. The forearm is in a neutral position and the elbow extended. The subject's feet are on the floor. The resistance with the hand held dynamometer is placed 1 inch just proximal to the elbow crease. The evaluator stabilizes at the top of the shoulder, avoiding contact with the anterior deltoid muscle. Evaluator should match the subject's resistance for at least two seconds before increasing their force to break the contraction. The number is recorded, the dynamometer is reset to zero, and the test repeated.

6.15.2.2. Elbow Flexion

The subject is seated in a hard back chair with their arm by their side, not resting on the armrest. The elbow is flexed to 90 degrees. The subject's feet are on the floor. The forearm is supinated. The hand held dynamometer is placed 1 inch proximal to the wrist.

The evaluator stabilizes at the posterior lateral elbow. Evaluator should match the subject's resistance for at least two seconds before increasing their force to break the contraction. The number is recorded, the dynamometer is reset to zero, and the test repeated.

6.15.2.3. Elbow Extension

The subject is seated in a hard back chair arm at the side with their arm at their side, not resting on the armrest and their elbow flexed to 90 degrees. The subject's feet are on the floor. The forearm is in neutral (thumb is pointing toward the ceiling) The hand held dynamometer is placed 1 inch proximal to the wrist on the ulnar (5^{th} finger) side. The evaluator stabilizes at the lateral elbow and applies force in an upward direction. Evaluator should match the subject's resistance for at least two seconds before increasing their force to break the contraction. The number is recorded, the dynamometer is reset to zero, and the test is repeated.

6.15.2.4. Wrist Extension

The subject is seated in a hard back chair with the elbow flexed to 90 degrees. The forearm is pronated and rests on the armrest. The wrist is neutral (not flexed or extended). The subject's feet are on the floor. The hand held dynamometer is placed just proximal to the metacarpal joints. The evaluator stabilizes at the lateral elbow. Do not allow elbow flexion. Evaluator should match the subject's resistance for at least two seconds before increasing their force to break the contraction. The number is recorded, the dynamometer is reset to zero, and the test repeated.

6.15.2.5. First Dorsal Interosseous

The subject is seated in a hard back chair with the elbow flexed to 90 degrees. The subject's feet are on the floor. The forearm is pronated and resting on the armrest, the index finger is abducted. The hand held dynamometer *with the finger attachment* is placed at the proximal interphalangeal joint on the lateral (thumb) side. The evaluator stabilizes at the wrist on the ulnar side proximal to the MCP. Take care not to exert a counter force with stabilizing hand. Evaluator should match the subject's resistance for at least two seconds before increasing their force to break the contraction. The number is recorded, the dynamometer is reset to zero, and the test repeated.

6.15.2.6. Hip Flexion

The subject is seated in a hard back chair with the hip flexed to 90 degrees. They should rest their hands in their lap or at their side, and not hold onto the chair. The subject must have adequate strength to flex their hip to the point where the back of their thigh comes off of the chair. The leg being tested is raised into hip flexion with the opposite foot on the floor. The hand held dynamometer is placed 1 inch proximal to the knee. The evaluator stabilizes at the lateral hip. The evaluator should match the subject's resistance for at least two seconds before increasing their force to break the contraction. The number is recorded, the dynamometer is reset to zero, and the test repeated.

6.15.2.7. Knee Extension

The subject is seated in a hard back chair with the hip flexed to 90 degrees and a towel roll is placed under the knee of the leg being tested. They should rest their hands in their lap or at their side, and not hold onto the chair. The knee partially extended to 45 degrees. The subject must have adequate strength to extend their knee into this position. The hand held dynamometer is placed 1 inch proximal to the ankle. The evaluator stabilizes behind the knee, just proximal to the knee joint. Evaluator should match the subject's resistance for at least two seconds before increasing their force to break the contraction. The number is recorded, the dynamometer is reset to zero, and the test repeated.

6.15.2.8. Knee Flexion

The subject is seated in a hardback chair with the hip flexed to 90 degrees and a towel roll placed under the knee of the leg being. They should rest their hands in their lap or at their side, and not hold onto the chair. The knee is partially extended to 45 degrees. The leg being tested is raised off the floor, with the opposite foot on the floor. The hand held dynamometer is placed 2 (two) inches proximal to the posterior ankle. The evaluator stabilizes at the anterior proximal knee joint to prevent hip flexion. The subject bends their knee against the resistance of the dynamometer. Evaluator should match the subject's resistance for at least two seconds before increasing their force to break the contraction. The number is recorded, the dynamometer is reset to zero, and the test repeated.

6.15.2.9. Ankle Dorsiflexion

The subject is seated in a hard back chair with the knee extended and the heel resting on a towel roll placed on the floor. They should rest their hands in their lap or at their side, and not hold onto the chair. The ankle is in 0 degrees (neutral) dorsiflexion (foot perpendicular to the lower leg). The opposite foot remains flat on the floor. The hand held dynamometer is placed proximal to the metatarsal joints on the dorsum of the foot just lateral to the great toe. The evaluator stabilizes at the anterior proximal knee joint. Evaluator should match the subject's resistance for at least two seconds before increasing their force to break the contraction. The number is recorded, the dynamometer is reset to zero and the test repeated.

6.15.3. Appendix 3: Procedure for IT transplantation of MSC-NTF cells

The purpose of this document is to describe the procedure and define the basic requirements for Intrathecal (IT) Transplantation of BrainStorm's proprietary MSC-NTF cells in clinical trials.

The procedure described here is based on common clinical practice (standard lumbar puncture procedure) as well as the experience of the medical staff currently conducting the company's clinical trial at the Neurology Department of the Hadassah Medical Center in Jerusalem.

6.15.3.1. Product Handling and injection procedures

All syringes should be gently rotated for 20-30 seconds until all cells are in suspension.

For IM injections remove syringe cap and connect a 25Gx5/8" (0.5 x 16 mm) needle.

With the needle in the upright position gently flick the syringe to surface any trapped bubbles. Push the plunger up until the first drop is visible at the tip of the needle. At this point the product is ready for injection.

For IT injections gently remove syringe cap. With the syringe in the upright position gently flick syringe to surface any trapped bubbles. Slowly and carefully push plunger up, until the liquid meniscus is visible at the top of the (needle-less) syringe. Connect syringe to the 3rd outlet of the valve, and inject the cells over roughly 2 minutes (see section 6.15.3.2. below).

6.15.3.2. IT Injection Procedure:

1. When performing IT transplantation of MSC-NTF cells, the patient is typically placed in a left (or right) lateral position with his/her neck bent in full flexion and knees bent in full flexion up to his/her chest, approximating a fetal position as much as possible.
2. The area around the lower back is prepped using aseptic technique. A 20 G, 3.5 inch, 0.9x90 mm spinal needle (such as: BD Cat. No. 405253) is inserted between the lumbar vertebrae L3/L4 or L4/L5 to a depth at which there is a "give" indicating that the needle is past the ligamentum flavum.
3. The needle is inserted further until there is a second 'give', indicating that the needle is now past the dura mater and in the subarachnoid space.
4. The stylet from the spinal needle is then withdrawn and a 3-way stopcock (such as Elcam Medical Cat. No. 582682) is immediately attached to the spinal needle.
5. A 3 to 5 ml syringe, with the plunger drawn back, is attached to the 2nd outlet of the stopcock, and approximately 3 ml of cerebrospinal fluid (CSF) is removed (CSF is not 'aspirated' since any negative pressure can be harmful, so the syringe plunger is drawn back before connecting the syringe, and the syringe with the drawn-back plunger is then connected to the 2nd outlet of the stopcock and the CSF thus flows into the syringe).
6. The syringe containing the CSF is removed and closed, the air is removed from the syringe and the syringe is then again placed at the 2nd outlet of the stopcock. The CSF is injected back only after the injection of the MSC-NTF as described below.
7. A second syringe containing a 4 ml suspension of MSC-NTF cells is attached to the 3rd outlet of the valve, and the cells are injected over roughly 2 minutes.
8. The stopcock is then immediately turned back to the 2nd outlet and approximately 1 ml of the previously collected CSF is injected, "washing" the spinal needle and ensuring that the entire cell suspension is transplanted into the patient.

9. The procedure is completed by withdrawing the needle and immediately placing pressure on the puncture site.
10. The syringe containing the remaining 2 mL of CSF is removed and capped and should be transferred to storage at -80ºC within 30 minutes of the completion of the procedure.
11. The patient is typically asked to lie on his/her back for at least 2 hours, on an anti-Trendelenburg position and is monitored for signs of neurological problems.

6.15.4. Appendix 4: Procedure for IM transplantation of MSC-NTF cells

The purpose of this document is to describe the procedure and define the basic requirements for Intramuscular (IM) transplantation of BrainStorm's proprietary MSC-NTF cells in clinical trials.

The procedure described here is based on common clinical practice (IM injection) as well as the experience of the medical staff currently conducting the company's clinical trial at the Neurology Department of the Hadassah Medical Center in Jerusalem.

6.15.4.1. Product Handling and injection procedures

All syringes should be gently rotated for 20-30 seconds until all cells are in suspension.

For IM injections remove syringe cap and connect a 25Gx5/8" (0.5x16mm) needle.

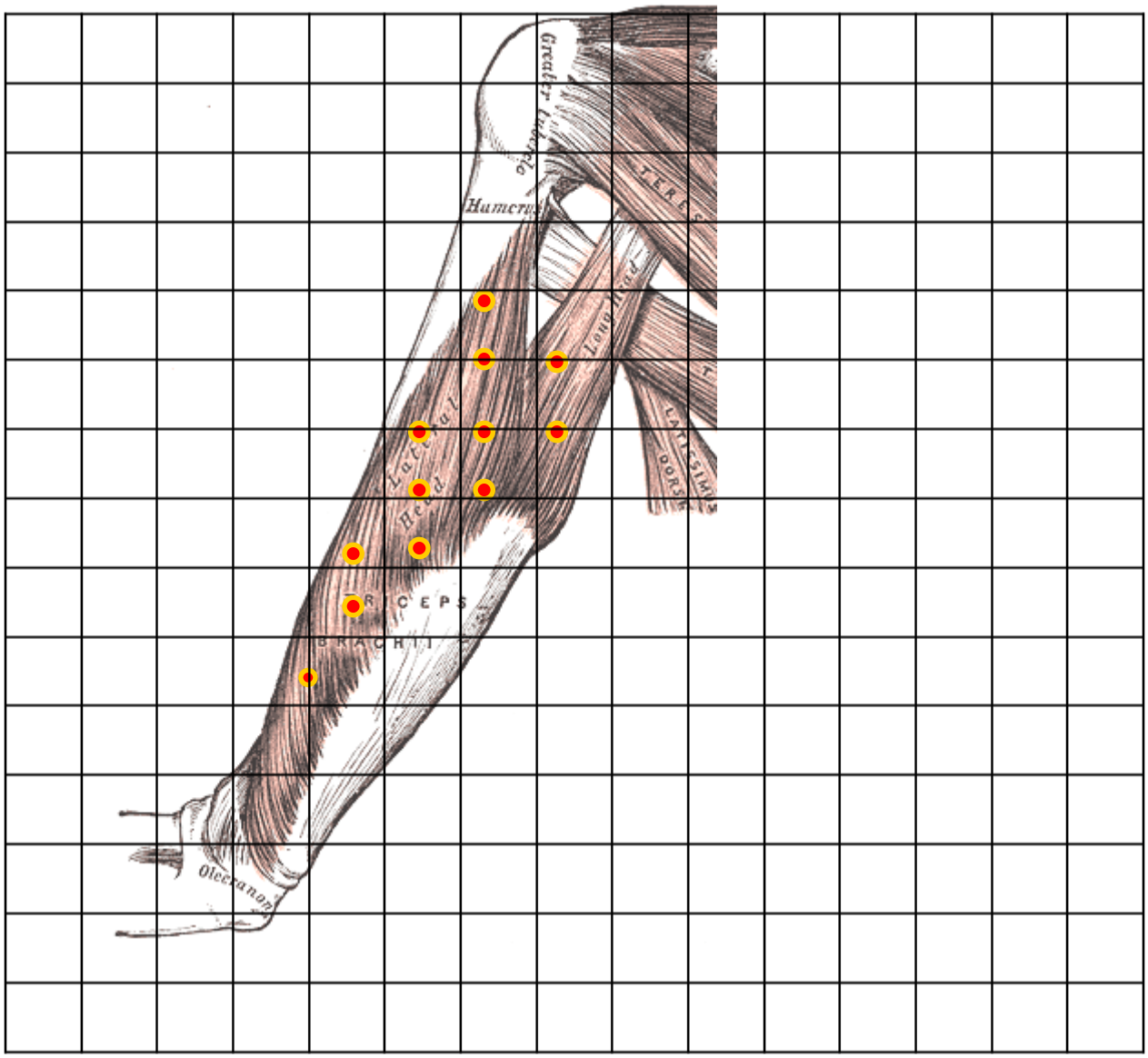
With the needle in the upright position gently flick the syringe to surface any trapped bubbles. Push the plunger up until the first drop is visible at the tip of the needle. At this point the product is ready for injection.

6.15.4.2. Procedure:

1. For IM transplantation of MSC-NTF cells, the patient may be in a reclining or upright position. The upper arm area is prepped using aseptic technique. In case of a hairy arm the arm is shaved prior to IM injections.
2. The syringes for IM injection contain an 0.32 ml suspension of MSC-NTF cells, in a 1 ml Luer-Lock syringe (such as: Becton Dickinson Cat. No. 309628), attached to a 25Gx5/8" (0.5 x 16 mm, such as Becton Dickinson Cat. No. 300600) needle.
3. The MSC-NTF cell suspension (0.2 ml) is transplanted into the patient by multiple intramuscular injections (IM) to a 1.5 cm depth (ensuring that injection is into the muscle and not into adipose tissue) at 24 separate sites on the patient's right upper arm biceps and triceps muscles, according to a map based on the designed grid (see below).
4. The procedure is completed by withdrawing the needle.
5. The patient's arm is bandaged with a pressure bandage
6. The patient is typically asked to remain in the clinic area for at least 2 hours, and is monitored for signs of neurological problems.

6.15.4.3. GRID FOR BICEPS & TRICEPS MUSCLES IM INJECTION

6.15.4.3.1. Grid of Triceps



6.15.4.3.2. Grid of Biceps