EDISON

BrainStorm Cell Therapeutics

Initiation of coverage

Designer stem cells targeting ALS

Pharma & biotech

BrainStorm Cell's (BCT) NurOwn enables extracted mesenchymal stem cells (MSCs) to express neurotrophic factors that can support cells affected by neurodegenerative diseases. Early work in amyotrophic lateral sclerosis (ALS) has shown signs of slowing down the rate of disease progression which, if replicated in the current US Phase II study, should lead to a marked re-rating given significant unmet medical need. Our rNPV valuation is $98m.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
12/13	0.0	(5.0)	(0.47)	0.0	N/A	N/A
12/14	0.0	(7.4)	(0.54)	0.0	N/A	N/A
12/15e	0.0	(9.1)	(0.50)	0.0	N/A	N/A
12/16e	0.0	(11.9)	(0.64)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding intangible amortisation, exceptional items and share-based payments.

Neurotrophic factors

The NurOwn process helps differentiate bone marrow-derived autologous (patient-derived) MSCs following extraction into neurotrophic factor (NTF) secreting cells (MSC-NTF), which are transplanted to the patient with the aim of treating neurodegenerative diseases. MSC-NTF cells release several neurotrophic factors, with the aim of aiding in cellular repair, neuron growth and re-establishing neural tissue connections in neurodegenerative conditions.

Slowing disease progression in Phase I/II ALS data

ALS, affecting about 12,000 people in the US, is a devastating condition impairing motor function and often causes death within two to five years. No current therapy materially improves outcomes. Two Israel-based, single-site MSC-NTF clinical studies in ALS showed safety and efficacy in terms of retarding progression using ALS symptom scales and measures of lung function.

US Phase II underway and multi-dose study planned

A 48-patient US Phase II study began in June 2014 and will provide a readout compared to a placebo-controlled group. Enrolment was completed in August 2015. As the company's eventual goal is to develop the product for repeat dosing as an ongoing therapy, the firm is planning a 24-patient, three-dose Phase II study in Israel, to start by y/e 2015. Data from both studies are expected in 2016 and could lead to a pivotal Phase III program in H216.

Valuation: rNPV of $98m; large market potential

We value BCT using a risk-adjusted net present value (rNPV) model, with a 12.5% cost of capital. Our valuation of $98m ($5.31/share excluding Q215 net cash) includes the prospects of NurOwn in ALS, assuming an H219 launch and 15% probability of success. Like most neurodegenerative conditions, ALS is a very challenging condition to treat, with many treatments having previously failed in trials, thus development risk remains elevated. BCT is assessing NurOwn for other neurological disorders, including progressive multiple sclerosis.

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Price	**US$3.13**
Market cap	**US$58m**

Net cash ($m) at Q215	19.7
Shares in issue	18.5m
Free float	87%
Code	BCLI
Primary exchange	NASDAQ
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	7.2	(17.0)	(26.9)
Rel (local)	8.7	(9.3)	(24.9)

52-week high/low	US$7.5	US$2.7

Business description

BrainStorm Cell Therapeutics is developing stem cell therapies designed to secrete neurotrophic factors that can aid in cell repair and function in neurological diseases. Its lead product, MSC-NTF (NurOwn) is in Phase II studies for amyotrophic lateral sclerosis (ALS).

Next events

Start Israel-based multi-dose Phase II ALS study	H215
Results from double-blinded, single-dose US Phase II ALS study	Mid-2016

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Edison profile page

Investment summary: Moving ahead in ALS

Company description: Neurotrophic stem cells

Established following a reverse merger with Wizbang Technologies, the firm in-licensed stem cell (SC) technologies from Tel Aviv University in 2004 and focused on developing SC-based treatments for neurological diseases. In 2010, it started human studies in Israel in amyotrophic lateral sclerosis (ALS) using a single dose of its autologous NurOwn stem cell therapy, designed to secrete neurotrophic factors. The company started a placebo-controlled US Phase II study in ALS in 2014 (results expected in mid-2016) and plans to start a multi-dose study in H215. While ALS is the company's most advanced indication and opportunity, it is also evaluating its SC technologies for other neurological indications.

Exhibit 1: Upcoming catalysts

Event	Timing
Commence multi-dose Phase II ALS study	H215
Complete enrolment of US Phase II ALS study	H215
Pre-IND meeting for candidate for progressive multiple sclerosis indication	Late 2015
Results from US Phase II ALS study	Mid-2016

Source: Company documents, Edison Investment Research

Valuation: rNPV of $98m reflects large ALS market opportunity

Our rNPV of $98m rNPV ($5.31 per share fully diluted, or $6.37 per share after including $19.7m Q215 net cash) applies a 12.5% cost of capital and assumes a 15% probability of success in ALS. We assume peak global sales in ALS of $1.05bn by 2025, reflecting the potential to capture 30% peak market share. Our valuation is higher than the current c $38m EV, and does not include NurOwn's prospects in other indications.

Financials: Further capital likely needed by year end 2016

BCT had $19.7m net cash on 30 June 2015 and its H115 cash burn rate was $3.6m. We expect the burn rate to increase as the US clinical trial continues and as BCT advances its multi-dose Israel study. We expect burn rates of $4.4m in H215 and $12.1m in 2016. We assume BCT will raise $30m by late 2016 to advance its programs and an additional $30m in 2018 to reach commercialisation in ALS. For illustrative purposes, we assign these fund-raisings to long-term debt.

Sensitivities: Funding, development risks, competition

While early open-label ALS studies have shown efficacy signals vs historical controls, ALS is a very heterogeneous disease and thus previous results could have been affected by patient selection. Results from larger controlled studies will be key, but altogether there remains significant development and regulatory risk for emerging therapeutics in neurodegenerative conditions such as ALS. An additional challenge will be sustaining access to capital at favourable terms to fund the ALS program through multiple clinical trials. Competing products (including alternative SC-based therapies) are also being developed for ALS and other indications BCT may pursue, and its commercial success will depend on relative performance vs potential competing new products.

Outlook : Stem cells for neurodegenerative diseases

BCT is developing an SC therapy using its proprietary and patented NurOwn process, which helps differentiate autologous MSCs following their extraction (eg bone marrow) into NTF secreting cells (MSC-NTF), which are then transplanted to the patient with the aim of treating neurodegenerative diseases. The MSC-NTF cells release several neurotrophic factors (NTFs),[1] with the aim of aiding cellular repair, neuron growth and re-establishing neural tissue connections to provide benefit in neurodegenerative conditions.

BCT's lead NurOwn program is in Phase II studies for the treatment of ALS, an often fatal, rapidly progressive and crippling condition with a prevalence of 12,000[2] in the US (and similar per-capita rates in Europe) that attacks neurons responsible for controlling voluntary muscles. BCT is also exploring applying this process for other neurological indications, such as progressive multiple sclerosis, and could begin human trials by H116. BCT's core technology was developed by researchers at Tel Aviv University and the company has a licensing agreement with the university's technology transfer arm (Ramot), whereby the latter will be entitled to 5% sales royalties.

MSCs could play key role in regenerative medicine

SCs are unspecialized cells that can multiply/reproduce (self-renew) and also differentiate into more specialized cell types. They are believed to be responsible for growth, wound healing and replacing cells that are lost or damaged through regular wear and tear and/or pathological conditions. MSCs are a subset of non-hematopoietic (non-blood cell) adult stem cells that originate from the mesoderm.[3] Numerous studies have shown that as MSCs arrive at damaged tissue sites, they interact with local stimuli (including inflammatory cytokines and ligands for toll-like receptors) to produce growth factors (including VEGF, HGF and others), which leads to tissue regeneration.[4]

MSCs can be easily isolated from the bone marrow, adipose tissue, the umbilical cord, muscle and lung.[4] MSCs are multipotent, meaning they can differentiate into multiple mesoderm cell lineages, including osteoblasts (bone cells), chondrocytes (cartilage cells), myocytes (muscle cells) and adipocytes (fat cells), as well as some ectodermic (including neuron-like cells) and endodermic cell types under special circumstances. Compared to pluripotent SCs or embryonic SCs, which can differentiate into a wider range of cell types, MSCs are far less likely to form tumors on implantation, making them presently much more amenable for SC-based regenerative medicine/therapeutic applications. This explains why MSCs are the most commonly used SCs in current clinical applications and trials.[4]

NurOwn uses autologous SCs rather allogeneic SCs

The NurOwn technology uses autologous SCs, which are administered back to the same person from whom they were harvested, rather than allogeneic SCs (whereby the cells are dosed to a different host, but from the same species as the source from which the cells were harvested). The potential advantage of autologous transplantation is that there is no projected risk of rejection or a

[1] These factors support neuron growth, survival and differentiation and include glial-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF).

[2] National Institute of Neurological Disorders and Stroke (part of NIH) http://www.ninds.nih.gov/disorders/amyotrophiclateralsclerosis/detail_ALS.htm.

[3] Mammalian cells are all derived from three germ layers. The ectoderm will form the nervous system, hair, epidermis of the skin, and other outer/surface structures. The mesoderm forms skeletal muscle, smooth muscle, the heart, blood vessels, blood cells, kidney, spleen, fat cells, the skeleton and most connective tissues and most of the urogenital system. The endoderm forms the epithelial lining of the gastrointestinal tract, as well as the liver, pancreas, gall bladder, thyroid and the respiratory surface of the lungs.

[4] Acta Pharmacologica Sinica (2013) 34: 747–754; doi: 10.1038/aps.2013.50.

need for treatment with immunosuppressive drugs (given that the patient's immune system would not be expected to react with the genetic make-up of the extracted/harvested cells). Allogeneic SCs carry the potential benefit of being able to administer off-the-shelf to the patient without requiring invasive extraction or sampling from the original patient. Some researchers suggest that allogeneic SCs may be less efficacious than autologous SCs. While all MSCs respond comparably to biochemical stimuli (to up- or down-regulate certain proteins), the specific response may rely on genotypical variations, and minor differences between host and donor cells may have an impact on trophic effects following MSC administration.[5]

Large unmet need for ALS

ALS often leads to progressive impairments in mobility and loss of independence and the ALS Association estimates mean survival following diagnosis at between two and five years. Part of the challenge for developing ALS therapies is that the condition's underlying etiology (cause and pathogenesis) can differ widely between individuals. ALS is a diagnosis for differing pathophysiologic mechanisms (ie for up to 20% it can be due to mutations in free radical scavenging enzyme superoxide dismutase 1, SOD1) that lead to a common outcome of progressive motor neuron loss. NurOwn is being developed for all forms of ALS. The only approved treatment is riluzole (Rilutek, Sanofi), a glutamate signalling inhibitor that extends survival time by two to three months.[6] Riluzole does not reverse existing nerve damage or muscle weakness, and studies differ on whether the drug shows benefit in preserving motor function.[7]

NurOwn Treatment protocol in ALS

The NurOwn treatment protocol involves harvesting undifferentiated MSCs from the patient via bone marrow aspiration. The extracted MSCs are isolated, propagated, and differentiated into NTF-secreting (MSC-NTF), which are then re-introduced into the same patient through intrathecal (IT) injection (i.e. into cerebrospinal fluid via simple lumbar puncture) and intramuscular (IM) injection. Several studies have suggested that direct SC injection or placement into a site of need or repair is the preferred method of treatment, as vascular delivery (ie through IM or intravenous) can be subject to a "pulmonary first pass effect" where many MSCs are sequestered or trapped in the lungs prior to reaching the desired target sites.[4] The rationale for IT administration is to deliver cells as close to the site of damage as possible without raising significant safety risks.

MSC-NTF clinical data in ALS show improvements in several measures

Two Israel-based, single-site MSC-NTF clinical studies in ALS were completed between 2010 and 2014. A 12-patient pilot, single-site Phase I/II study used IT (for six late-stage ALS patients) or IM dosage (for six patients with earlier-stage disease). A Phase IIa trial enrolled 14 subjects in three ascending-dose cohorts receiving a single MSC-NTF dose delivered through both IM and IT administration.[8] Both studies had a three-month run-in period before patients received the single MSC-NTF dose (the required bone marrow was aspired during this period). They showed good safety and tolerability, and that patients with IT treatment (all within the Phase IIa and six from the I/II trial) had improvements compared to historical controls using the ALS Functional Rating Scale (ALSFRS-R). This scale for evaluating the functional status of patients with ALS is used to monitor functional change in a patient over time. Improvements were shown vs historical controls in Forced

[5] Experimental & Molecular Medicine (2013) 45, e54; doi:10.1038/emm.2013.94.

[6] According to FDA Prescribing Information http://products.sanofi.us/rilutek/rilutek.pdf.

[7] Cochrane Database Syst Rev. 2007 Jan 24;(1):CD001447.

[8] The low-dose cohort (n=4) received 1.0m cells/kg IT and 24.0m cells IM (in the upper arm); the mid-dose cohort (n=6) received 1.5m cells/kg IT and 36.0m cells IM; the high-dose cohort (n=4) received 2.0m cells/kg IT and 48.0m cells IM.

Vital Capacity (FVC), a measure of lung function often used in ALS patients given that respiratory failure is often the cause of ALS mortality. Throughout the normal course of ALS progression, ALSFRS-R and FVC scores tend to worsen (reflecting condition deterioration) from baseline in a linear fashion. Exhibit 2 shows that for three- and six-month periods post-dosing, the rates of change (monthly slope) of ALSFRS-R score and FVC-level deteriorations for those receiving IT MSC-NTF doses was well below the baseline (initial three-month run-in) rate. These rates were also well below the historical rates shown in the PRO-ACT database of previously reported ALS clinical study data, which reflects the subgroups of placebo-treated patients with baseline ALSFRS-R scores above 35 (n=1,339) or FVC above 65% (n=1,662). Hence, treatment appeared to slow progression. Pooled analysis of all per-protocol treated patients in both studies who received IT administration (n=15) showed a 50% reduction in the ALSFRS-R slope at six months post treatment (-0.6 vs -1.2 in the three-month run-in), reflecting a p-value of 0.052.

Exhibit 2: Rate of progression in ALSFRS-R and FVC scores in clinical studies from those receiving IT doses

	Baseline score	Monthly slope (run-in)	Monthly slope (at three months)	Monthly slope (at six months)
ALSFRS-R				
Phase I/II (IT dose, n=6)	24.8	-1.56	-0.98	-0.28
Phase IIa (IT+IM, n=14)	39.9	-1.41	-0.78	-0.60
Pooled data, per protocol (n=15)		-1.2		-0.6 (p=0.052)
PRO-ACT (natural history)	40.5	-0.83	-0.84	-0.81
FVC (% predicted)				
Phase I/II (IT dose, n=6)	59.5	-3.48	-4.35	-2.30
Phase IIa (IT+IM, n=14)	87.3	-2.60	-0.70	-0.86
Pooled data, per protocol (n=15)		-5.20		-1.2 (p=0.036)
PRO-ACT (natural history)	90.6	-1.18	-1.40	-2.19

Source: Edison Investment Research, company documents

There were two deaths and two serious adverse events (AEs), which were unrelated to treatment. The majority of remaining AEs were low-grade and suggested an acceptable safety profile.

Placebo-controlled US Phase II study ongoing

The lack of blinding could have introduced observer or responder bias in the previous studies. A double-blinded study can provide a more objective assessment of treatment efficacy. A 48-patient, double-blinded, three-site US Phase II study began in June 2014 (NCT02017912). The trial will evaluate the safety and efficacy of a single combined IM and IT administration of MSC-NTF cells in early-stage ALS patients (baseline ALSFRS-R scores must be above 30). During the three-month run-in period, patient bone marrow will be harvested and MSCs will be isolated and expanded. Patients will be transplanted with their autologous MSC-NTF cells or placebo (36 to receive MSC-NTF, 12 placebo).

The efficacy endpoints will be the change in ALSFRS-R and SVC (slow vital capacity) slopes from the pre-transplantation period, as compared between the treatment and placebo groups through 24 weeks post-transplantation. Results from this trial are expected in mid-2016.

Multi-dose MSC-NTF Israel study planned

As the eventual goal is to develop NurOwn for repeat dosing as an ongoing therapy, the firm is planning to start a 24-subject, repeat-dose Phase II study in Israel in H215. Patients will receive three separate IT doses (totalling 125m cells), dosed two months apart. The firm plans to harvest all the autologous MSCs to be used for the three dosing rounds during a single bone marrow aspiration. Thus, unlike the previous studies, whereby “fresh” MSCs are used for MSC-NTF doses administered to the patient, this study will employ cryopreservation (“freezing”) for storing the MSCs initially extracted from the patient, which will then be “thawed” and prepared for processing into MSC-NTF doses at bimonthly treatment intervals. BCT anticipates its proprietary cryopreservation method will enable long-term MSC storage to allow for the production of repeat (up to 12) MSC-

NTF patient doses through a single bone marrow aspiration. However, some researchers found that, possibly due to the shock involved with freezing/thawing, biological properties of cryopreserved MSCs may differ from those of fresh or "growth phase" MSCs, potentially adversely affecting their efficacy.[9] Some suggest that 20-30% of thawed MSCs are compromised.[10] BCT indicates that its process includes an equilibration period for MSCs post-thawing prior to MSC-NTF differentiation, which it believes should greatly reduce the risks of post-thaw deleterious effects.

Exhibit 3: Competition review; selected Phase II and III NMEs in development for ALS

Product	Company	Mechanism	Current stage	Notes
Masitinib	AB Science	Small-molecule inhibitor of stem cell factor receptor tyrosine kinase (c-Kit; CD117); Drug rationale is cross-talk between microglia, mast cells and astrocytes may destroy motor neurons in ALS; preclinical studies suggest masitinib may reduce microglia proliferation, astrocyte migration and reduce motor neuron death.	Phase III	381-pt, placebo-controlled Phase III study underway; interim data expected Q116; primary endpoint is to detect a difference in ALSFRS-R between masitinib and placebo at week 48.
Tirasemtiv	Cytokinetics	Skeletal muscle (sarcomere) activator, stimulating fast skeletal muscle troponin complex by increasing calcium sensitivity.	Phase III	445-pt VITALITY-ALS Phase III started H215 with data expected H117; primary endpoint will be 24-week change from baseline in SVC vs placebo; tirasemtiv reduced the decline of slow vital capacity in 711-pt Phase IIb study, but did not improve ALSFRS decline rate.
TW001 (oral edaravone)	Treeway BV	As ALS may be associated with superoxide dismutase (SOD) mutations/dysfunction, TW001 is developed as antioxidant, to prevent damage to nerve cells caused by oxygen-containing molecules, and reduce inflammation.	Phase II/III	Phase III in planning stages; may commence in 2016.
GM604	Genervon Pharma	Endogenous embryonic-stage peptide binding to a subunit of insulin receptor (INSR), insulin-like growth factor-1 (IGF-1) receptor IGF1R and IGF2R; hypothesis is to aid neural cells development, differentiation and repair.	Phase IIA	Seven of eight evaluable patients from Phase IIA open-label trial had deceleration or cessation of disease worsening at 10 weeks post-dosing; firm in discussions with FDA for next trial and has filed for accelerated approval.
Ozanezumab	GSK	Humanised IgG monoclonal antibody against Nogo-A protein, an inhibitor of neurite outgrowth.	Phase II	304-pt, double-blinded Phase II with biweekly IV dosing for 48 weeks; efficacy endpoint ALSFRS-R and results to be announced in H215.
Ibudilast	MediciNova/ Kyorin	Oral small molecule phosphodiesterase (PDE) -4 and -10 inhibitor and macrophage migration inhibitory factor (MIF) inhibitor, to suppress pro-inflammatory cytokines, promote neurotrophic factors and attenuate activated glia cells.	Phase II	60-pt, double-blinded Phase II assessing ALSFRS-R at six months; results near year end 2015.
Acthar gel (repository corticotropin)	Mallinckrodt	ACTH injection expected to stimulate corticosteroid production to suppress immune response and potentially reduce neuro-inflammation.	Phase II	40-pt, eight-week open label trial Phase II with 28-week open-label extension; data expected H215.
NSI-566 (human spinal cord stem cells, HSSCs)	Neuralstem	Make synaptic contact with the host motor neurons and express neurotrophic growth factors to protect host motor neurons.	Phase II	15-pt open label Phase II reported in Q115 showed 47% response rate (7/15) at nine months, as measured by either near-zero ALSFRS slope decline or positive slope, or improved grip strengthening; larger Phase II study planned for H215.
NP001	Neuraltus	Reducing neuroinflammation by regulation of macrophage activity within the CNS.	Phase II	136-pt Phase II completed in 2012 did not meet primary endpoints of ALSFRS-R vs placebo, but post-hoc analyses of patients with higher baseline inflammation showed benefit; confirmatory Phase II study is planned.
sNN0029	Newron Pharma	Recombinant human VEGF 165 (rhVEGF165), aiming to block genes causing motor neuron death.	Phase II	VEGF treatment slowed disease progression in animal models. 18-pt European Phase II study with continuous treatment via implantable brain catheter started in Jan 2015, with data due in 2016.
HYNR-CS	Corestem	Autologous bone marrow-derived mesenchymal stromal cells (MSCs).	Phase I/II	Two-part Phase I/II study near completion; first step was 7-pt pilot study with patients dosed with two IT MSC doses 26 days apart, showed limited ALS progression at 12-months; second step is 72-pt semi-double blinded group, with data expected in H215.
VM202	ViroMed	PCK vector encoding hepatocyte growth factor (HGF) gene, to stimulate angiogenesis (new blood vessels).	Phase I/II	18-pt open-label Phase I/II underway; data including ALSFRS-R expected H215.
PXT-864	Pharnext	Proprietary combination of baclofen and acamprosate, intending to restore balance between excitatory and inhibitory neurotransmitter pathways.	Phase I/II	Currently in Phase II for Alzheimer's disease; Phase IIa in ALS is in planning stages.

Source: Edison Investment Research, BioCentury

[9] François M, Copland IB, Yuan S, et al. Cytotherapy. 2012 Feb;14(2):147-52. doi: 10.3109/14653249.2011.623691. Epub 2011 Oct 27.

[10] Galipeau J. Cytotherapy. 2013 Jan;15(1):2-8. doi: 10.1016/j.jcyt.2012.10.002.

AB Science's masitinib, already approved in the EU/US for mast cell tumors, expects Phase III ALS data in early 2016. Cytokinetics' tirasemtiv, which showed improvements in lung function (SVC) in earlier studies, expects pivotal data in H117. However, tirasemtiv did not improve ALSFRS-R scores in Phase II studies, which could limit its commercial appeal. There are also some other firms studying SCs, including MSCs. BCT believes that MSC-NTF can be potentially more effective than "conventional" MSCs for ALS, given that in addition to whatever other benefits "conventional" MSCs may provide (immunomodulation), MSC-NTF also provides NTFs intended to provide direct benefit to the damaged/dying neurons. BCT indicates that in its animal neurodegenerative disease model comparisons between MSC-NTF cells and MSCs, the MSC-NTF cells outperformed MSCs.

Neuralstem's NSI-566 uses human spinal cord stem cells (HSSCs) and has shown some efficacy in a Phase IIa study. Neuralstem claims that NSI-566 HSSCs can integrate and make synaptic contact with host neurons and replace dying neurons. This approach differs from MSC-NTF, which provides a generally more supportive environment for the existing surviving neurons. Given their differing mechanisms, in theory, both approaches could potentially be used simultaneously in ALS patients.

Longer-term measures to control COGS and scale up manufacturing

For the current US trial, BCT is manufacturing MSC-NTF in clean room facilities at universities associated with the clinical trial sites. These facilities are not cost-viable for commercial-stage production (current COGS c $30,000 per dose), so BCT is seeking a contract manufacturer to carry out scale-up activities for a potential pivotal study (in H216 or 2017). It also has a collaboration with Canada-based Octane Biotech to develop a potentially scalable NurOwn bioreactor and announced a successful initial prototype in mid-2014. BCT expects the next prototype to be delivered at around year-end 2015. Between these two approaches, BCT is confident that it is likely to be able to maintain its commercial-scale COGS at less than $10,000 per dose.

BCT MSCs for multiple sclerosis and autism

BCT is assessing the potential development of MSC-NTF for other neurological disorders, including progressive multiple sclerosis (MS) and autism. It is planning to have a pre-IND meeting with FDA officials in late 2015 for a therapeutic candidate in progressive MS. MSCs administered in a murine neural injury MS model have been shown to promote endogenous repair.[11] In a third-party pilot human study, 10 MS patients received autologous, expanded BM MSCs by IT injection. Five out of seven patients showed improvement in Expanded Disability Status Scale (EDSS) at six months.[12] In early 2015, BCT reported positive results from internal preclinical studies of NurOwn in the BTBR mouse, an established mouse model for autism.

Broad stem cell therapy competitive landscape

Several firms are exploring SC-based treatments, including in ALS and other neurodegenerative diseases. While there is still no US FDA-approved SC product, Prochymal was approved in Canada and New Zealand to treat children with steroid-resistant, graft-versus-host disease. While some firms are, like BCT, advancing MSC-derived therapies, other cell types are under evaluation, including mesenchymal precursor cells (believed to be the precursors of adult MSCs) by Mesoblast. The following exhibit summarizes many of the more advanced SC trials underway.

[11] Bai L, Lennon DP, Eaton V, et al. Human bone marrow-derived mesenchymal stem cells induce Th2-polarizedimmune response and promote endogenous repair in animal models of multiple sclerosis. Glia 2009; 57: 1192–1203.

[12] Yamout B, Hourani R, Salti H, et al. Bone marrow mesenchymal stem cell transplantation in patients with multiple sclerosis: a pilot study. J Neuroimmunol 2010; 227:185–189.

Exhibit 4: Selected participants in stem cell therapy competitive landscape

Company	Product	Cell source – type	Per dose range	Delivery	Lead indication	Status
Allogeneic (off the shelf)						
Mesoblast/Teva	Revascor	Bone marrow – mesenchymal precursor cells (MPC)	150m cells	Transendocardial injection	Congestive heart failure	1,165-pt Phase III
Osiris Therapeutics (Mesoblast)	Prochymal (remestemcel-L)	Bone marrow – mesenchymal stem cells (MSC)	150-300m cells	Intravenous infusion	Crohn's disease	330-pt Phase III
TiGenix	Cx-601	Adipose tissue – mesenchymal stem cells	120m cells	Intralesional injection	Crohn's disease (anal fistulas)	278-pt Phase III
Athersys	MultiStem	Bone marrow – multipotent adult progenitor cells	1bn cells	Intravenous infusion	Ischaemic stroke	Mixed efficacy in 108-pt Phase II
Capricor	CAP-1002	Heart tissue	25m cells	Intracoronary infusion	Acute myocardial infarction	274-pt Phase I/II
Pluristem Therapeutics	PLX-PAD	Placenta – mesenchymal-like adherent stromal cells	100-300m cells	Intramuscular injection	Intermittent claudication	150-pt Phase II
ReNeuron	ReN001	Brain tissue – neural stem cells (CTX line)	20m+ cells	Brain injection	Ischaemic stroke/CLI	41-pt Phase II
Neuralstem	**NSI-566**	**Spinal cord – neural stem cells**	**200,000-400,000 cells**	**Cervical, lumbar and brain injections**	**Amyotrophic lateral sclerosis**	**15-pt Phase II completed; new study planned**
Stemedica Cell Technologies	Stemedyne	Bone marrow – mesenchymal stem cells	0.5-1.5m cells/kg (~40-125m)	Intravenous infusion	Ischaemic stroke	35-pt Phase I/II
StemCells	HuCNS-SC	Spinal cord – neural stem cells	20m cells	Spinal cord injection	Spinal cord injury	50-pt Phase II
SanBio	SB623	Bone marrow – mesenchymal stem cells	2.5-10m cells	Brain injection	Ischaemic stroke	18-pt Phase I/IIa
Ocata Therapeutics	hESCs + MSCs	Human embryo stem cells and adult bone marrow MSCs	0.05m-0.2m cells	Subretinal injection	Macular degeneration and Stargardt's Macular Dystrophy	16-pt and 16-pt Phase I
ViaCyte	VC-01	Human embryo – human embryonic stem cells (hESCs)	-	Subcutaneous implant	Type 1 diabetes	40-pt Phase I/II
Autologous (patient-derived)						
Baxter	CD34+ stem cells	Bone marrow – CD34+ endothelial progenitor stem cells	1m cells/kg (~75m)	Endocardial catheter (Noga)	Chronic myocardial ischemia	291-pt Phase III
Celyad	C-Cure (C3BS-CQR-1)	Bone marrow – cardiac progenitor cells	600m cells	C-Cath catheter	Advanced chronic heart failure	240-pt Phase III
Cytori Therapeutics	ADRC	Adipose tissue – stromal vascular fraction cells	40m ADRCs (two injections per digit on both hands)	Subcutaneous injection	Scleroderma	80-pt Phase III
Bioheart	Myocell	Skeletal muscle tissue – myoblasts (muscle stem cells)	400-800m cells	Intramyocardial injection catheter	Congestive heart failure	170-pt Phase II/III
Samsung Medical Center	MSCs	Bone marrow – mesenchymal stem cells (expanded with autologous ischaemic serum)	-	Intravenous infusion	Ischaemic stroke	60-pt Phase III
Aastrom Biosciences	Ixmyelocel-T	Bone marrow – CD90+ mesenchymal cells, CD14+ monocytes	100-150m cells	Endocardial catheter (Noga)	Dilated cardiomyopathy	108-pt Phase II
NeoStem	AMR-001	Bone marrow – CD34+/CXCR4+ cells	10m cells	Intracoronary infusion	Acute myocardial infarction	160-pt Phase II
BrainStorm Cell Therapeutics	**NurOwn**	**Bone marrow – mesenchymal stem cells (secreting neurotrophic factors)**	**Up to 50m cells per dose IM; up to 2m cells/kg IT**	**Intramuscular injection**	**Amyotrophic lateral sclerosis**	**48-pt Phase II**

Source: Edison Investment Research, clinicaltrials.gov

Financial forecasts in ALS

We assume that BCT will start a pivotal 200-to 300-patient Phase III NurOwn ALS program in H216 or 2017. Data should be available by H218, and commercialisation is expected to start in H219 (NurOwn has FDA Fast Track status in ALS). We define the target market at 13,000 ALS patients in the US and over 20,400 in Europe (comparable with current prevalence figures and adjusted for population growth). We refrain from assuming dominant (>50%) market share to account for the possibility that other emerging ALS products may also reach the market. We assume the product will reach 30% peak US market share by 2025, and 21% peak market share in Europe, with generic competition starting in 2029. We assume that NurOwn patients will receive four doses per year and the initial net US selling price of each NurOwn dose will be $30,000. We assume initial COGS of $10,000 per dose (inclusive of the 5% royalty to be paid to Ramot).

Exhibit 5: Financial forecasts for NurOwn sales in ALS

	2019e	2020e	2021e	2022e	2023e	2024e	2025e
US market							
ALS prevalence	13,075	13,272	13,472	13,675	13,882	14,091	14,304
Market share	0.1%	1.3%	4.1%	9.8%	18.3%	26.2%	30.0%
Treatments per year per patient	4	4	4	4	4	4	4
Total number of treatments	59	678	2,185	5,380	10,167	14,760	17,164
Net revenue per treatment ($)	30,000	30,450	31,025	31,645	32,256	32,897	33,536
Total ALS US revenue ($000)	1,773	20,649	67,782	170,255	327,941	485,551	575,632
EU market							
ALS prevalence	20,493	20,803	21,116	21,435	21,758	22,087	22,420
Market share	0.1%	0.9%	2.8%	6.9%	12.8%	18.3%	21.0%
Treatments per year per patient	4	4	4	4	4	4	4
Total number of treatments	65	744	2,397	5,903	11,155	16,194	18,833
Net revenue per treatment ($)	22,500	22,837	23,269	23,734	24,192	24,673	25,152
Total ALS EU revenue ($000)	1,459	16,992	55,777	140,100	269,857	399,552	473,678
Worldwide ALS revenue ($000)	3,232	37,641	123,559	310,356	597,798	885,104	1,049,311

Source: Edison Investment Research

Valuation

Our BCT valuation includes the prospects of NurOwn in ALS. We apply a risk-adjusted net present value (rNPV) model, with a 12.5% cost of capital and a 15% probability of success. The company indicates that it plans to bring NurOwn to market in ALS without a commercial partner. Our model uses a similar assumption, given our view that substantial marketing resources and expertise may not be required to reach the majority of ALS clinics and treating physicians.

Exhibit 6: rNPV assumptions

Probability-weighted Contributions	Indication	rNPV ($m)	rNPV/share ($)	Probability of success	Launch year	Peak US market share	Peak worldwide sales (US$m)
NurOwn revenue	ALS	246.7	13.35	15%	2019	30%	$1.05bn in 2025
Cost of goods		(84.6)	(4.58)				
SG&A and Marketing expenses		(33.4)	(1.81)				
R&D Costs		(5.6)	(0.30)				
Net capex, NWC & taxes		(25.1)	(1.36)				
Total rNPV		98.1	5.31				
Net cash (debt) (Q215)		19.70	1.07				
Total equity value		117.7	6.37				
FD shares outstanding (000) (Q215)		18,481					

Source: Edison Investment Research

Our $98m rNPV assumption represents upside to BCT's current EV of c $38m. After including $19.7m Q215 net cash, our equity valuation of $118m equates to $6.37 per share fully diluted. The

following table shows how the equity valuation (including Q215 net cash) responds to differing success probabilities and peak market share assumptions.

Exhibit 7: Per-share equity value sensitivity analysis – probability of success vs peak US ALS market share

Peak market share	15%	30%	45%
5%	0.46	1.82	3.19
15%	2.39	6.37	10.35
25%	4.19	10.64	17.09

Source: Edison Investment Research

We note that our model includes material R&D costs for NurOwn ALS development, including $18-20m in annual R&D costs in 2017 and 2018 but, due to our discount rate and 15% probability of success assumptions, the discounted amount of future R&D costs in our rNPV valuation is $5.6m.

Sensitivities

Development and regulatory risk: to gain approval, NurOwn must deliver efficacy in pivotal, randomized studies without significant safety concerns. Clinical data to date have come from small open-label studies and, given that ALS is a heterogeneous disease, meaningful development risks remain. The cryopreservation/thawing processes could reduce the number of viable MSC-NTF cells and thereby increase the dosages needed to deliver the desired efficacy, which could adversely affect COGS. NurOwn COGS must be contained to ensure profitability without weakening market share.

Competition considerations: competing products (including SC-based therapies) are being developed for ALS; commercial success will depend on relative performance.

Financing risk: BCT will require additional funds to develop NurOwn through commercialization in ALS. We assume current funds on hand will last into Q416 and that BCT will need to raise an additional $60m over the following three years for clinical, regulatory and commercial activities to reach commercialisation in ALS. While we assume the company will be able to raise debt to fund these requirements, it may need to raise equity instead, at issue pricing that may not be favourable for current shareholders and could lead to significant dilution.

Intellectual property risk: the success of NurOwn will depend on BCT's ability to defend the IP assets surrounding its technologies. The company has US patent 8,663,987 (expiring in 2029) covering its stem cells induced to secrete large quantities of neurotrophic factors for the treatment of neurodegenerative disease, and US patent 8,647,874 (expiring in 2027) covering the proprietary production methods for such cells (as well as a European patent also covering similar IP).

Financials

On 30 June 2015, BCT had $19.7m in cash and equivalents and no debt. Its H115 cash burn rate (operating cash flow minus net capex) was $3.6m. In January 2015, BCT raised c $13m (gross) from the exercise of warrants (2.5m shares exercised at $5.22 per share). We expect the burn rate to increase as the US clinical trial continues and as BCT advances its multi-dose Israel study and programs for other indications. We expect an H215 burn rate of $4.4m and a 2016 burn rate of $12.1m. We assume the company will raise $30m by late 2016 to advance its programs and $30m in 2018. For modelling purposes, we assign these financings to long-term debt.

Exhibit 8: Financial summary

US$(000)	2013	2014	2015e	2016e	2017e
31-December	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	0	0	0	0	0
Cost of Sales	0	0	0	0	0
General & Administrative	(2,126)	(2,649)	(3,948)	(4,145)	(4,353)
Research & Development	(2,917)	(4,772)	(5,320)	(7,900)	(21,200)
EBITDA	(5,043)	(7,421)	(9,268)	(12,045)	(25,553)
Depreciation	0	0	0	0	0
Amortization	0	0	0	0	0
Operating Profit (before exceptionals)	(5,043)	(7,421)	(9,268)	(12,045)	(25,553)
Exceptionals	144	(1,825)	67	0	0
Other	0	0	0	0	0
Operating Profit	(4,899)	(9,246)	(9,201)	(12,045)	(25,553)
Net Interest	0	0	140	159	(99)
Profit Before Tax (norm)	(5,043)	(7,421)	(9,128)	(11,886)	(25,651)
Profit Before Tax (FRS 3)	(4,899)	(9,246)	(9,061)	(11,886)	(25,651)
Tax	0	0	0	0	0
Profit After Tax and minority interests (norm)	(5,043)	(7,421)	(9,128)	(11,886)	(25,651)
Profit After Tax and minority interests (FRS 3)	(4,899)	(9,246)	(9,061)	(11,886)	(25,651)
Average Number of Shares Outstanding (m)	10.7	13.7	18.4	18.5	18.5
EPS - normalised ($)	(0.47)	(0.54)	(0.50)	(0.64)	(1.39)
EPS - normalised and fully diluted ($)	(0.47)	(0.54)	(0.50)	(0.64)	(1.39)
EPS - (IFRS) ($)	(0.46)	(0.68)	(0.49)	(0.64)	(1.39)
Dividend per share (C$)	0.0	0.0	0.0	0.0	0.0
BALANCE SHEET					
Fixed Assets	280	333	402	612	843
Intangible Assets	0	0	0	0	0
Tangible Assets	280	333	402	612	843
Current Assets	4,446	9,578	15,401	33,305	7,422
Short-term investments	0	4,290	94	94	94
Cash	3,503	4,251	15,193	33,097	7,214
Other	943	1,037	114	114	114
Current Liabilities	(1,332)	(3,113)	(2,526)	(2,526)	(2,526)
Creditors	(1,332)	(3,113)	(2,526)	(2,526)	(2,526)
Short term borrowings	0	0	0	0	0
Long Term Liabilities	(655)	(123)	0	(30,000)	(30,000)
Long term borrowings	0	0	0	(30,000)	(30,000)
Other long term liabilities	(655)	(123)	0	0	0
Net Assets	2,739	6,675	13,277	1,391	(24,261)
CASH FLOW					
Operating Cash Flow	(4,054)	(4,487)	(8,035)	(12,045)	(25,553)
Net Interest	0	0	140	159	(99)
Tax	0	0	0	0	0
Capex	(108)	(161)	(116)	(210)	(231)
Acquisitions/disposals	(5)	1	0	0	0
Financing	3,584	10,285	14,757	0	0
Net Cash Flow	(583)	5,638	6,746	(12,096)	(25,882)
Opening net debt/(cash)	583	(3,503)	(8,541)	(15,287)	(3,191)
HP finance leases initiated	0	0	0	0	0
Other	4,669	(600)	0	0	0
Closing net debt/(cash)	(3,503)	(8,541)	(15,287)	(3,191)	22,692

Source: Company documents, Edison Investment Research

Contact details	Revenue by geography
BrainStorm Cell Therapeutics Three University Plaza Drive Suite 320 Hackensack, NJ 07601 +1 201 488 0460 www.brainstorm-cell.com	N/A

Management team

Chief Executive Officer: Chaim Lebovits	Executive Scientific Advisor (elect): Dr Tony Fiorino
Appointed CEO in September 2015, having served as President of BCT since July 2007; during this period Mr Lebovits also served as principal executive officer of BCT (August 2013 to June 2014). He is also chairman and CEO of ACC Holdings International, an investment company with several holdings in biotech and natural resources.	Succeeded by Chaim Lebovits as CEO in September 2015, having served as CEO of BCT since June 2014; Dr Fiorino will remain at BCT in an executive scientific role. Before joining BCT, he was an MD at Greywall Asset Management, a healthcare equity fund. Previously, he was founder, president and CEO of EnzymeRx, where he oversaw the acquisition of a preclinical biologic and its development through Phase I/II studies before its subsequent sale to 3SBio. Before founding EnzymeRx, Dr Fiorino worked as a biotechnology and pharmaceuticals analyst and portfolio manager at companies including JP Morgan, Citigroup and Pequot Capital. He has an MD and PhD from the Albert Einstein College of Medicine and a BS from the Massachusetts Institute of Technology.
Chief Financial Officer: Yoram Bibring	**Vice-President, Scientific and Regulatory Affairs: Yael Gothelf**
Mr Bibring joined BCT as CFO in July 2014, having previously served as the CFO at Sapiens North America. Before Sapiens, he served as the CFO for Silenseed, a clinical-stage biopharmaceutical company, and before that he was the CFO for Healthcare Corporation of America. He previously also held CFO positions at Fundtech and several Israeli high-tech companies. Mr Bibring holds a Bachelor of Science in Accounting and Economics from Tel Aviv University and is a Certified Public Accountant.	Dr Gothelf has more than 15 years' experience in the biotechnology industry. At BCT she is responsible for regulatory compliance, clinical trials, product development and intellectual property. Before joining the company in 2007, she was the scientific manager of the Research & Process Development Division of InterPharm Laboratories, a subsidiary of Ares-Serono. Previously, she was a researcher at the Molecular and Cell Biology Department of the Weizmann Institute of Science, where she also completed her post-doctorate fellowship. She holds a PhD from Tel Aviv University.

Principal shareholders	(%)
ACCBT Corp	10.5
Sabby Management LLC	4.0
Vanguard Group	2.3
Perceptive Advisors LLC	2.2
Aigh Investment Partners	2.0

Companies named in this report

Octane Biotech, Sanofi, AB Science, Cytokinetics, Neuralstem, Mesoblast