Autologous Transplantation of Mesenchymal Stem Cells Secreting Neurotrophic Factors (NurOwn®) In ALS: Results of a Phase 2 Clinical Trial

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Objective

To evaluate the safety and efficacy of transplantation of NurOwn® (MSC-NTF cells), autologous bone marrow-derived mesenchymal stem cells (MSC) induced to secrete neurotrophic factors (NTFs), in amyotrophic lateral sclerosis (ALS). ClinicalTrials.gov identifier: NCT01777646.

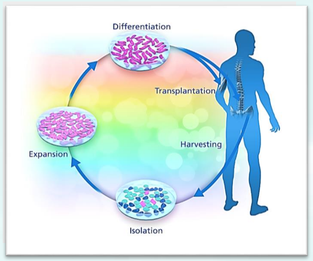
Background

MSC-NTF cells secreting GDNF, BDNF, VEGF and HGF have been shown to have neuroprotective effects *in-vitro* and in animal models of neurodegenerative diseases, including ALS. A prior phase 1/2 study showed a single intrathecal (IT) or intramuscular (IM) administration of MSC-NTF cells to be safe and well tolerated, and several subjects receiving IT administration showed stabilization of ALSFRS scores.

Design/Methods

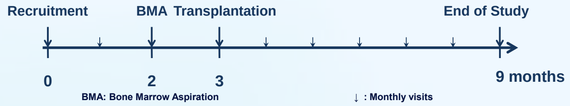
The study enrolled 14 ALS patients in three ascending dose cohorts. During a three month run-in period, ALS Functional Rating Score-Revised (ALSFRS-R) and forced vital capacity (FVC) were assessed monthly and bone marrow-derived MSC were isolated, expanded *ex-vivo* and induced to secrete NTFs. Subjects then received a single dose of MSC-NTF cells via IT and IM administration to the right biceps and triceps, and were followed for safety and efficacy measures, including ALSFRS-R and FVC, for six months after administration

The NurOwn® Technology



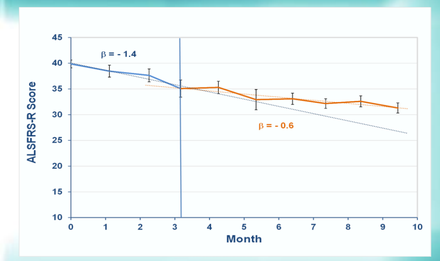
Study design: Combined IT + IM transplantation
Escalating Dose: 14 patients

Dose	Low	Medium	High
Number of patients	4	6	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



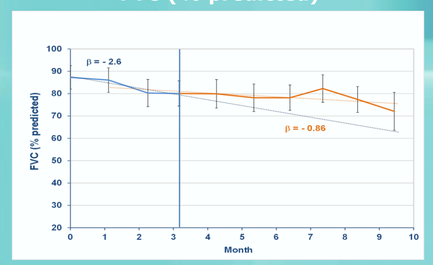
Results

Mean ALSFRS-R Score



Mean ± SEM of the ALSFRS-R score over time. The vertical blue line indicates time of treatment; β indicates the pre- and post treatment slope.

FVC (% predicted)



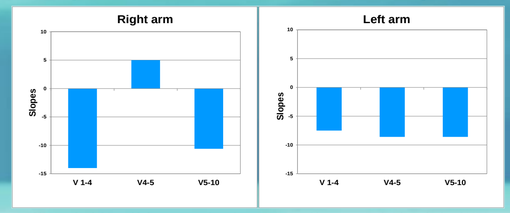
Mean ± SEM of the FVC (% predicted) over time. The vertical blue line indicates time of treatment; β indicates the pre- and post treatment slopes.

Progression Rate for all IT-Treated Subjects in Phase 2a and Prior Phase 1/2 Study

	Pre-Treatment (per month)	Post-Treatment (per month)	p value
6 month follow-up (n=15)			
ALSFRS-R	-1.2	-0.6	0.052
FVC (% predicted)	-5.1%	-1.2%	0.036

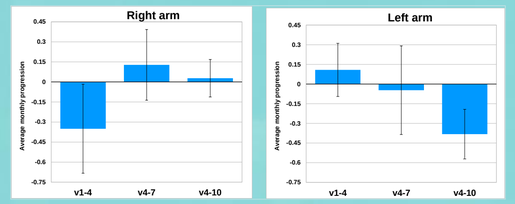
A piecewise linear regression model was generated based on data of all IT-treated subjects who completed 6 months follow up in the current study and a prior phase 1/2 study with a similar design (ClinicalTrials.gov identifier: NCT01051882)

Changes in Arm Muscle Volume by MRI-Based 3D Volumetric Analysis



Change in right and left arm muscle volume assessed by computerized analysis of MRI scans of ALS patients for the run-in period, and for 1 and 6 months post-treatment.

Change in CMAP of the Musculocutaneous Nerve

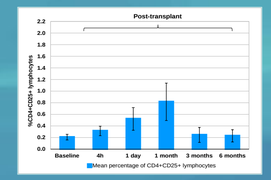


Monthly progression of compound muscle action potential (CMAP) of right and left biceps as measured by EMG for the run-in period, and for 3 and 6 months post-treatment.

ALSFRS-R or FVC Responders (from those with completed follow-up)

	3 Month Post-Treatment	6 Month Post-Treatment
ALSFRS-R	6/12	5/10
FVC (% predicted)	8/12	6/10
ALSFRS-R or FVC	11/12	9/10

Change in Peripheral CD4+ CD25+ Lymphocytes



Safety Summary

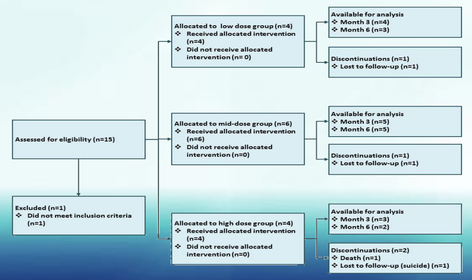
Pt. #	Adverse Event	Outcome
001	Headache, back/leg pain	Resolved
002	General weakness	Resolved
003	Fever, headache,vomiting, tachycardia, leg spasticity	Resolved
004	Headache	Resolved
005	Back/leg pain, fever	Resolved
006	Headache, Back pain, fever	Resolved
007	Headache, back/pelvis/leg pain, fever, vomiting	Resolved
008	Headache	Resolved
010	Headache, back/leg pain, fever	Resolved
011	Fever, headache, back pain	Resolved
012	Headache, back/pelvis/leg pain, vomiting, fever, death	*Physician assisted suicide
013	Hyponatremia Sudden death	* Not related to tx
014	Headache, fever	Resolved
015	Headache, back, leg/back pain, fever, neck stiffness	Resolved

No treatment related SAEs observed. All adverse events resolved within 1-2d

Conclusions

- The study met its primary objective in demonstrating that a single simultaneous intrathecal (up to 2 million cells/kg) and intramuscular (up to 48 million cells to the upper arm) administration of MSC-NTF cells was safe and well-tolerated.
- A strong efficacy signal was observed as subjects in the study experienced a clinically meaningful reductions in their rate of disease progression, as assessed by both ALSFRS-R and FVC, for 6 months after treatment.
- A piecewise linear regression model of these data pooled with results from our earlier phase 1/2 study revealed a statistically significant reduction in the rate of FVC decline (p=0.036) and a nearly significant reduction in the rate of ALSFRS-R decline (p=0.052) for the 6-month post treatment period.
- The results of theses studies indicate that MSC-NTF cells show promise as a potential treatment for ALS, and possibly other neurodegenerative diseases.

Subject Disposition



Demographic data

Patient#	Gender	Age	ALS FRS
1*	M	45	34
2	M	34	40
3	M	23	38
4	M	41	46
5	F	51	41
6	F	55	39
7	F	58	39
8	M	59	41
10**	M	52	42
11	M	62	41
12*	F	58	42
13***	F	64	37
14	M	55	37
15	F	55	39
Mean±SD		50.8±11.4	39.7±2.9