BrainStorm Cell Therapeutics
US clinical trial
BCT-001-US

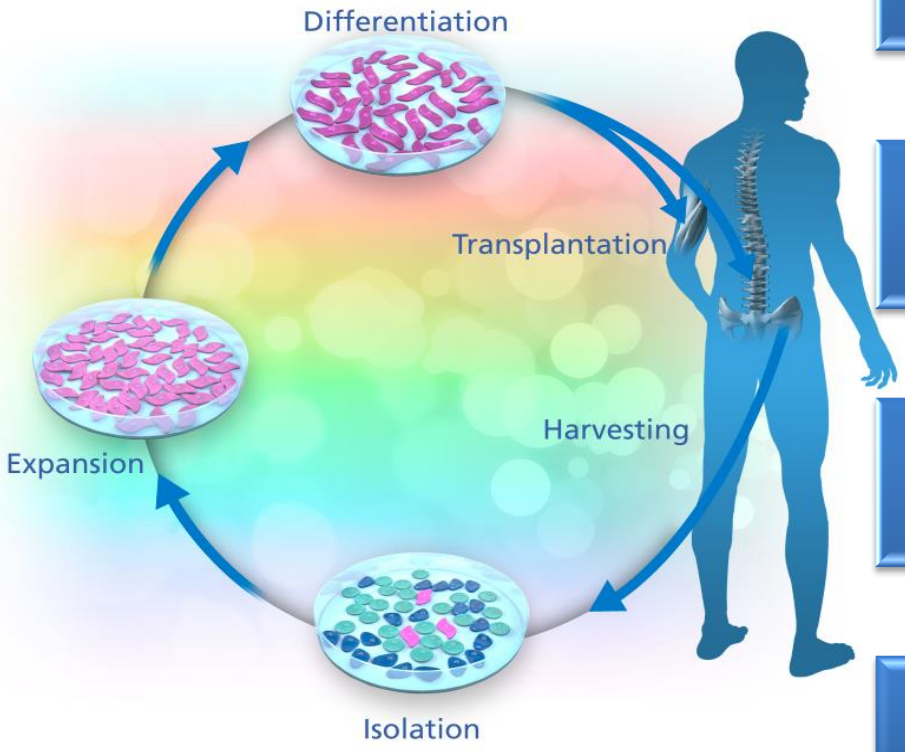
A Phase 2, Randomized, Double Blind, Placebo Controlled Multicenter Study to Evaluate Safety and Efficacy of Transplantation of Autologous Mesenchymal Stem Cells Secreting Neurotrophic Factors in Patients With Amyotrophic Lateral Sclerosis

Presented by:

James D. Berry, MD, MPH and Robert H. Brown, MD, DPhil

December 9th 2016

The MSC-NTF cells (NurOwn®) Technology



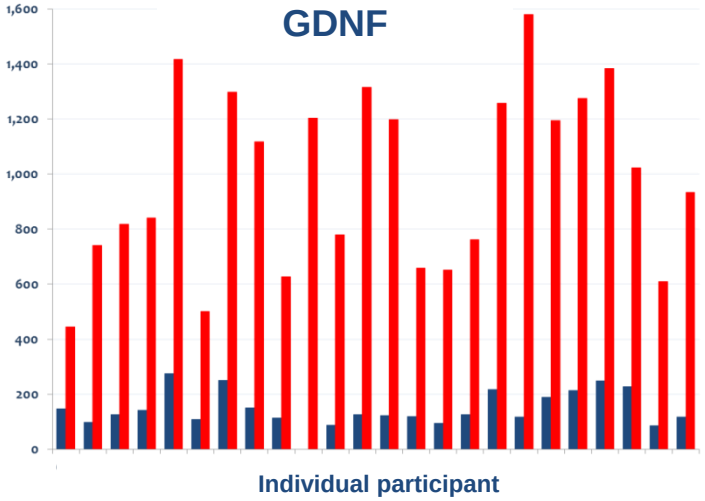
Bone marrow is harvested and MSCs are isolated from the total bone marrow population

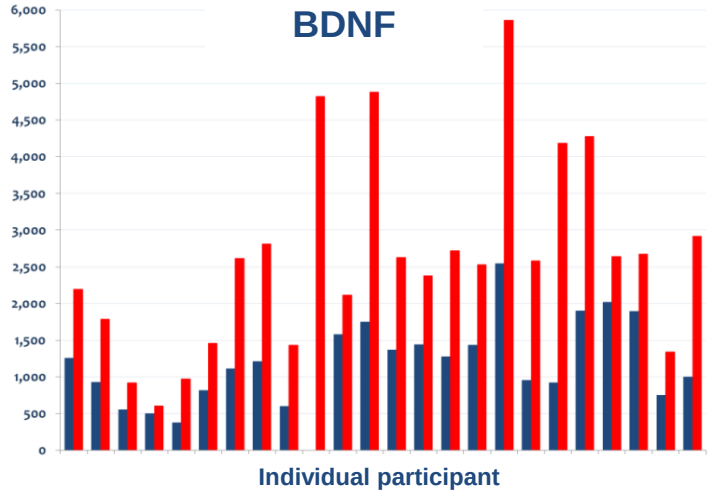
MSCs are expanded *ex-vivo*

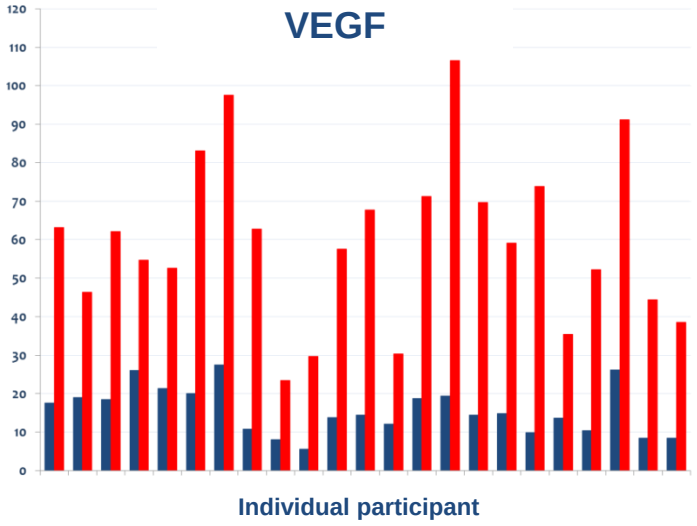
MSC are induced to differentiate

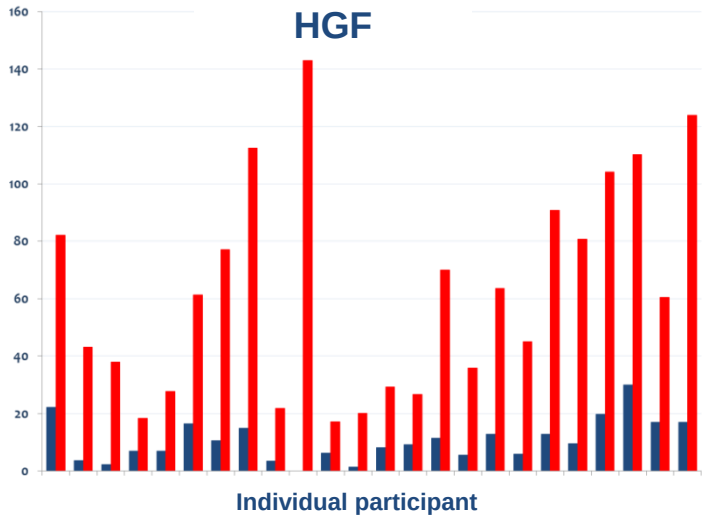
MSC-NTF cells are transplanted back into the patient by IT and/or IM administration

Bone marrow-derived MSC-NTF cells of ALS cases show enhanced growth factor secretion *in-vitro*









Pilot studies of MSC-NTF in ALS showed safety and possible benefit

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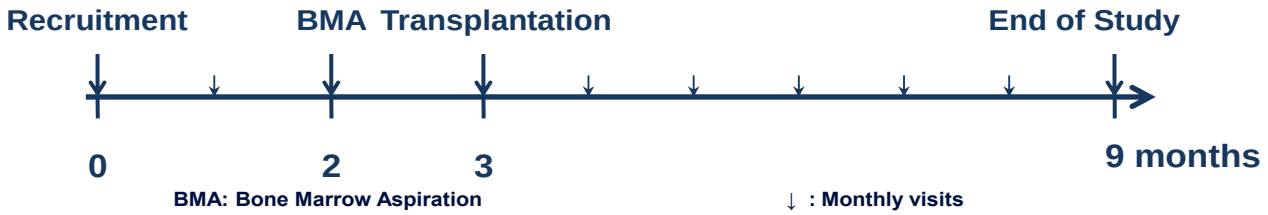
Study 1

Cohort	Number of Subjects	Route of Administration	Number of Injection Sites	Site of Administration	Dose
Early ALS	6	Intramuscular (IM)	24	Biceps and triceps muscles	1 x 10^6 cells/site
Advanced ALS	6	Intrathecal (IT)	1	Cerebrospinal fluid (CSF)	1 x 10^6 cells/kg

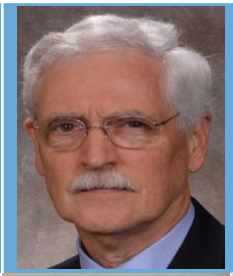
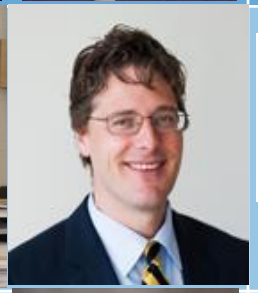
Study 2

Cohort	Number of Subjects	Route of Administration	Number of Injection Sites	Site of Administration	Dose
Low	4	IM +	24	Biceps and triceps	1 x 10^6 cells/site
		IT	1	CSF	1 x 10^6 cells/kg
Medium	6	IM +	24	Biceps and triceps	1.5 x 10^6 cells/site
		IT	1	CSF	1.5 x 10^6 cells/kg
High	4	IM +	24	Biceps and triceps	2 x 10^6 cells/site
		IT	1	CSF	2 x 10^6 cells/kg



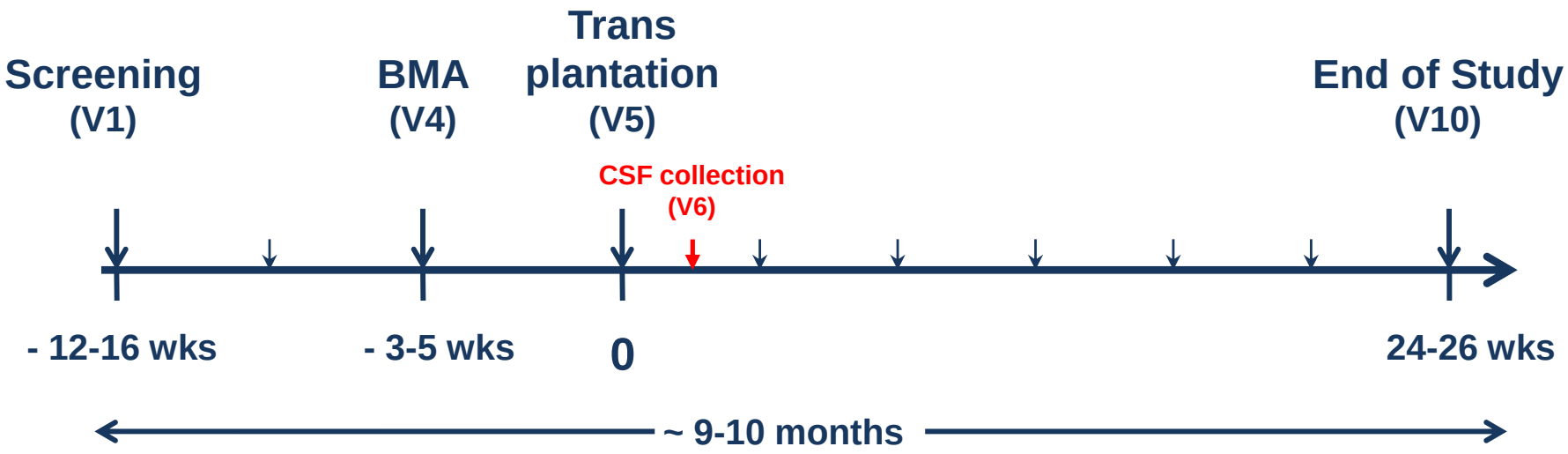
BCT-001-US Clinical Trial of MSC-NTF in ALS

Three clinical trial sites:

Principal Investigators			Medical Center
Professor Robert H. Brown Dr. Ayo Owegi			University of Massachusetts Medical School
Professor Merit Cudkowicz Dr. James Berry			MASSACHUSETTS GENERAL HOSPITAL
Professor Anthony Windebank Dr. Nathan Staff			MAYO CLINIC

BCT-001-US Clinical Trial Study Design

- 48 participants (16 per site)
- Randomized 3:1
- Intervention
  - IM: 24 injections (12 into R biceps, 12 into R triceps); 2 million cells each
  - IT: 125 million cells in 4mL
- Inpatient Observation for 48 hours
- Evaluators remained blinded. Different Unblinded team delivered cells/placebo.



BMA: Bone Marrow Aspiration

↓ Monthly visits

BCT-001-US Clinical Trial of MSC-NTF in ALS Endpoints

- **Primary:**
  - **Safety and tolerability**
- **Secondary:**
  - **ALSFRS-R**
  - **Slow vital capacity (SVC)**
- **Exploratory:**
  - **Muscle strength (HHD)**
  - **CSF Biomarkers (added after the 1st 8 participants)**

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RESULTS

Baseline Characteristics were balanced

Disposition/Demographics	MSC-NTF (N=36)	Placebo (N=12)
Male (%)	25 (69.4)	10 (83.3)
Mean Age (SD)	50.3 (11.9)	53.5 (9.11)
El Escorial Criteria		
Possible	3 (8.3)	1 (8.3)
Laboratory-Supported Probable	5 (13.9)	1 (8.3)
Probable	16 (44.4)	7 (58.3)
Definite	12 (33.3)	3 (25.0)
Months Since ALS Diagnosis – Mean (SD)	9 (5.6)	9 (4.6)
Months Since first symptom– Mean (SD)	18 (3.8)	17 (3.1)
Completed*	33 (91.7)	10 (83.3)
Discontinued Follow-up	3 (8.3)	2 (16.7)

* ITT analyses included all participants

Ref. Tables 14.1.1.1, 14.1.2.2

Treatment with Cells Appears Safe and Tolerable

- No deaths
- No treatment-related SAEs
- No AEs led to dropouts
- Common Adverse Events (Most Mild/mod severity):

Adverse Event	MSC-NTF (%)	Placebo (%)
Headache and Procedural Headache	80.6	66.7
Back Pain	72.2	8.3
Pyrexia	33.3	0
Arthralgia	33.3	0
Injection Site Pain	27.8	8.3
Constipation	25	8.3
Pain in Extremity	22.2	0
Neck Pain	19.4	0
Myalgia	16.7	0
Cough	16.7	0
Nausea	16.7	0

- Post-therapy SAEs related to disease progression (e.g. G-tubes) were more frequent in the MSC-NTF cells group.

Ref. Table 14.3.1.2

Safety Conclusions

Carlayne E. Jackson, MD, FAAN, Professor of Neurology and Otolaryngology, Chief Medical Officer - UT Medicine San Antonio, University of Texas Health Science Center who served as the chair of the Data Safety Monitoring Board on this study:

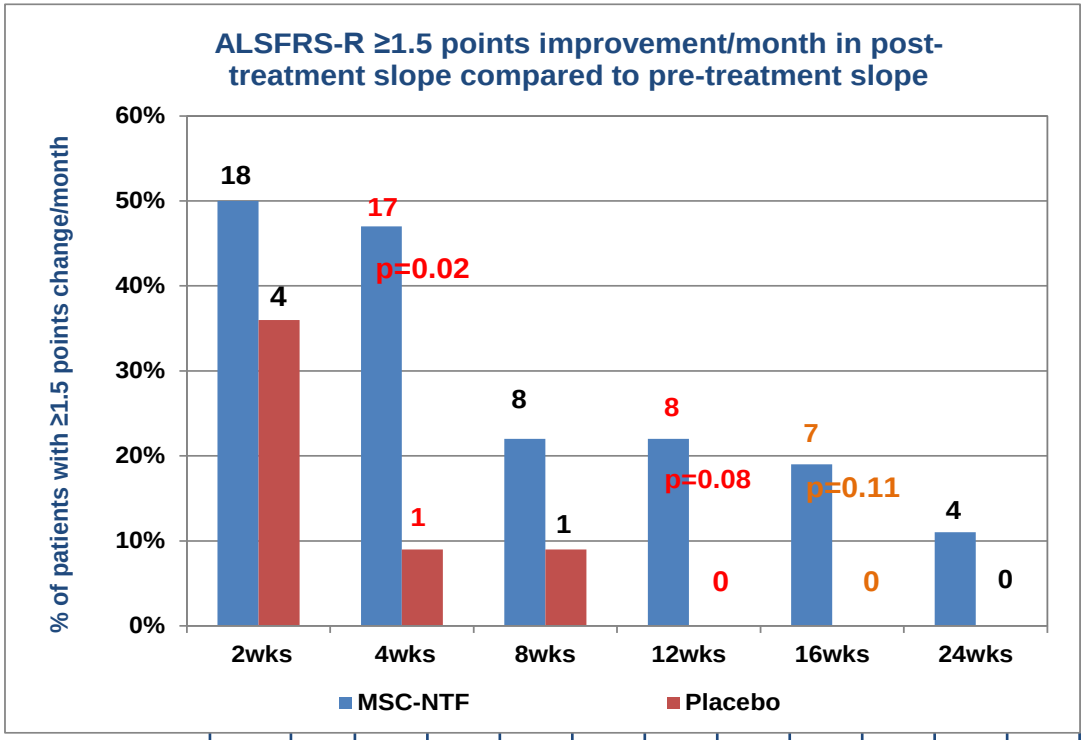
"Patients in the Brainstorm study tolerated treatment extremely well and there were no serious adverse events related to therapy. The safety profile certainly provides the opportunity to continue to study this approach to ALS treatment"

BrainStorm's press release, July 18th 2016

Pre-specified ALSFRS-R efficacy analyses in Statistical Analysis Plan

- **Mean change in slope pre- *vs* post-treatment**
- **Responder Analysis (% of subjects with slowing post-tx)**
- **Subgroup analyses**
  - **Excluding slow progressors**
    - **"Slow" defined as ≤ 2 points decline in ALSFRS-R from screening to baseline**
  - **Baseline SVC ≥ 70%**
- **Two-sided alpha = 0.20 for analyses of means and one- sided 0.10 for responder analyses**

More people in the cell therapy group were responders (Point improvement on ALSFRS-R)



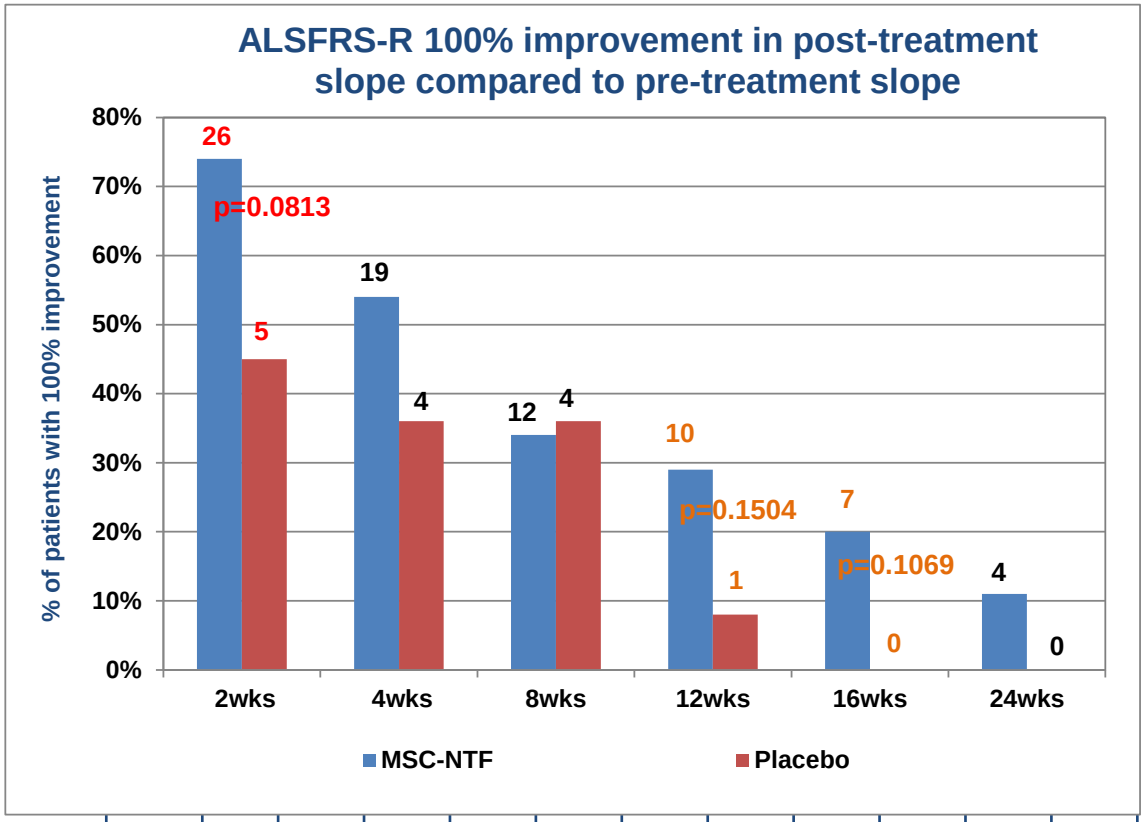
18 of 36	4 of 11	17 of 36	1 of 11	8 of 36	1 of 11	8 of 36	0 of 12	7 of 36	0 of 12	4 of 36	0 of 12
T	P	T	P	T	P	T	P	T	P	T	P
2wks		4wks		8wks		12wks		16wks		24wks	

p-values using one-sided Fishers Exact Test

Given the exploratory nature of this study, statistical significance was defined as a one-sided p value <0.1 (these p-values are highlighted in red above). In order to see trends in the data p-values that are ≥ 0.1 and < 0.2 are also highlighted in orange

Ref. Table 14.2.1.28

More people in the cell therapy group were responders (Halt of ALSFRS-R decline or improvement)



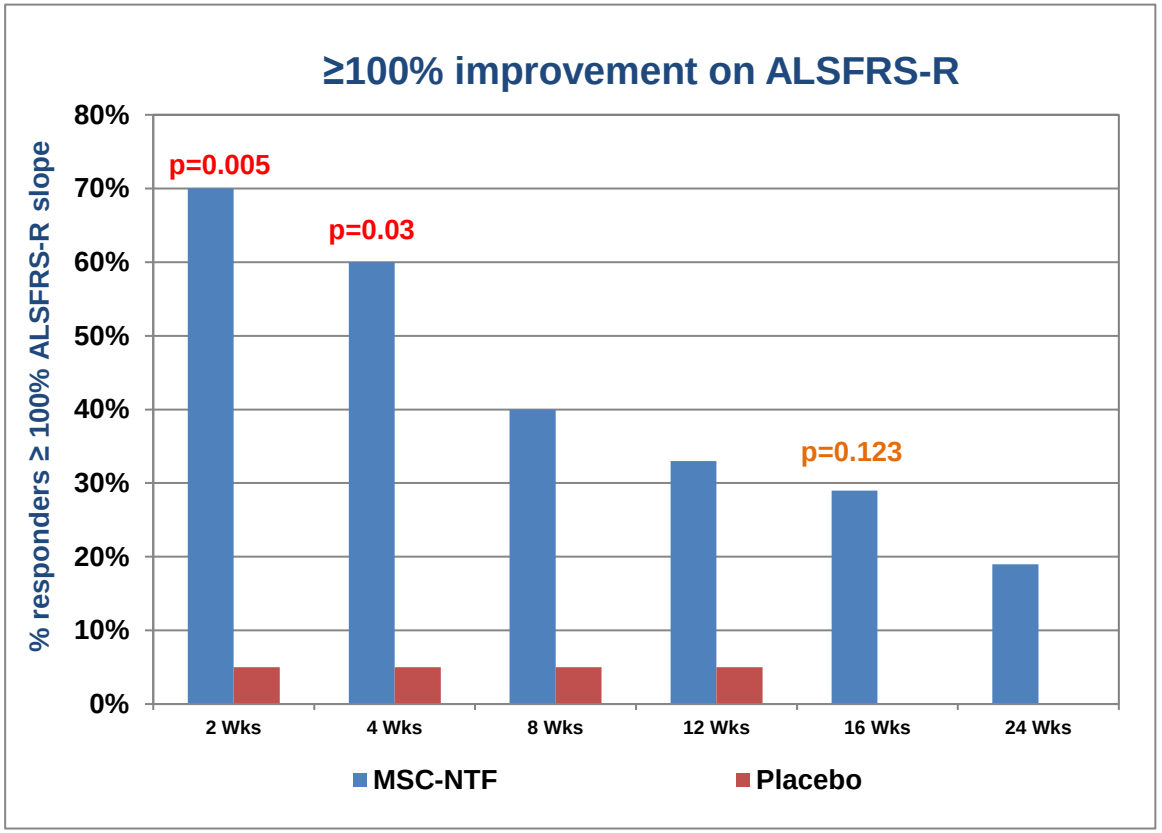
26 of 35	5 of 11	19 of 35	4 of 11	12 of 35	4 of 11	10 of 35	1 of 12	7 of 35	0 of 12	4 of 35	0 of 12
T	P	T	P	T	P	T	P	T	P	T	P
2wks		4wks		8wks		12wks		16wks		24wks	

T – Treatment; P – Placebo

one-sided p value <0.1 (these p-values are highlighted in red above)
p-values that are ≥ 0.1 and < 0.2 are also highlighted in orange

Ref. Table 14.2.1.26

Excluding slow progressors
Many more people in the cell therapy group were responders (Halt of ALSFRS-R decline or improvement)

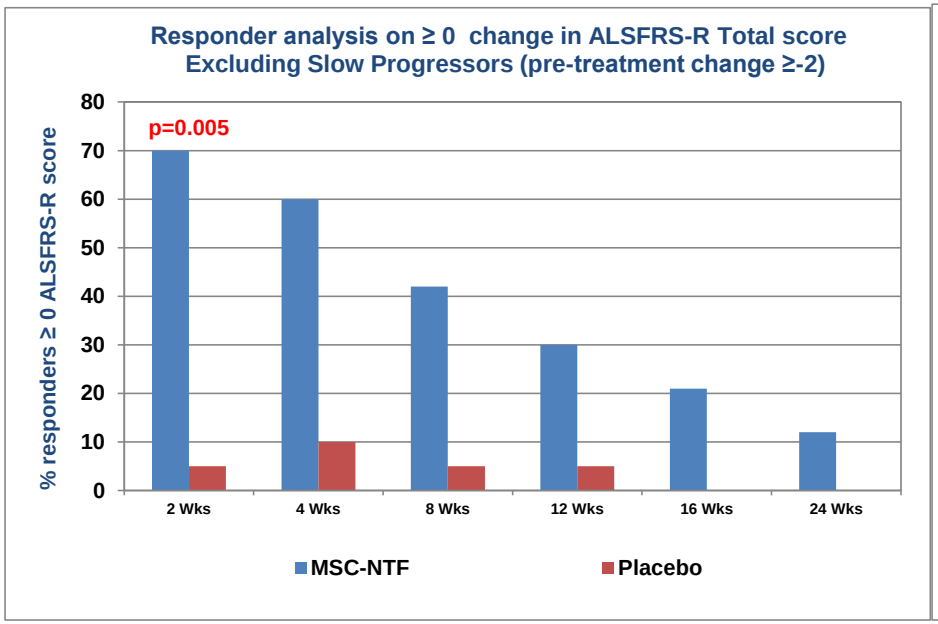


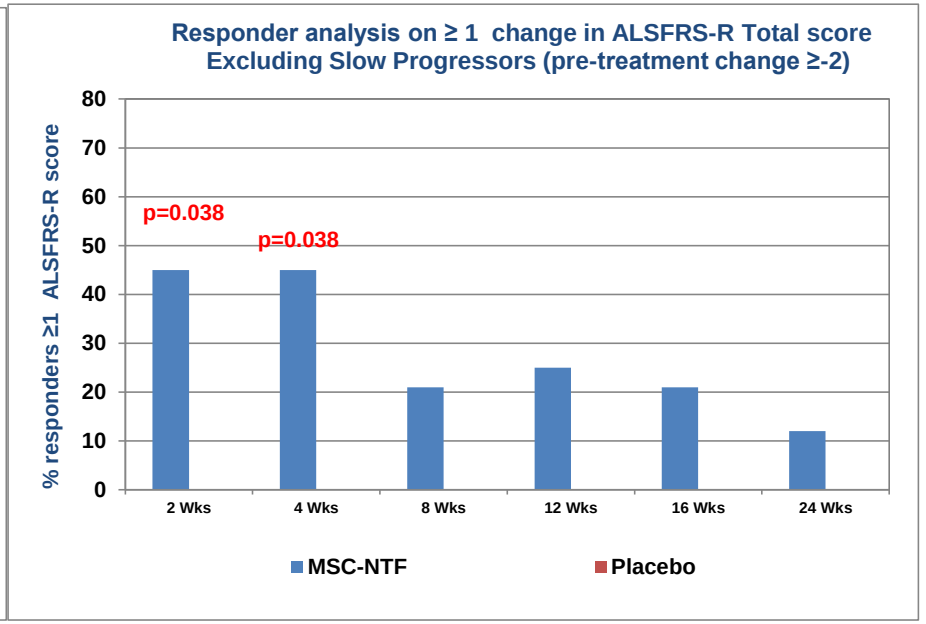
p-values are one-sided from Fisher's Exact test

one-sided p value <0.1 considered significant (exploratory study)

Ref. Table 14.2.11.2

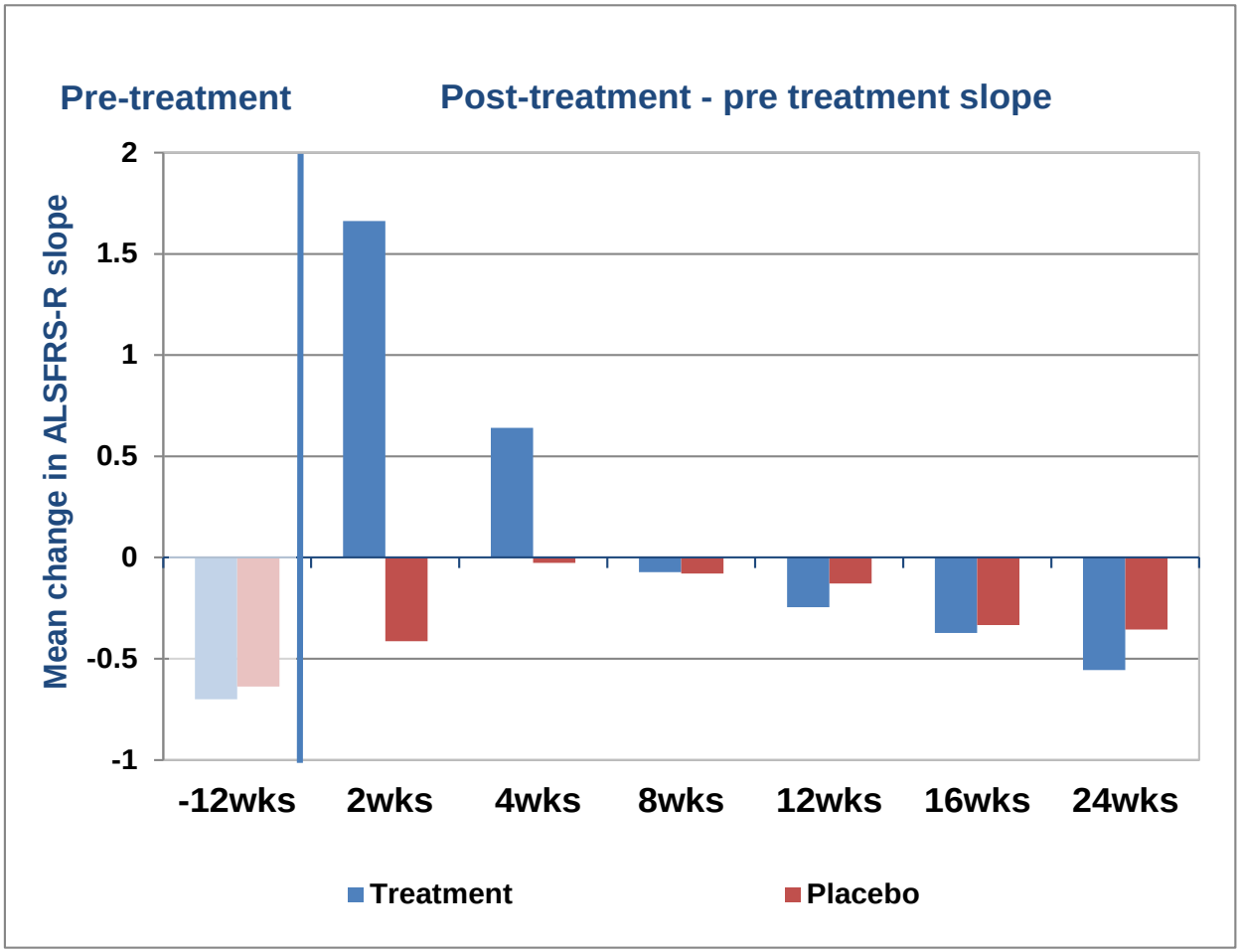
Responder analysis on change in ALSFRS-R score excluding slow progressors





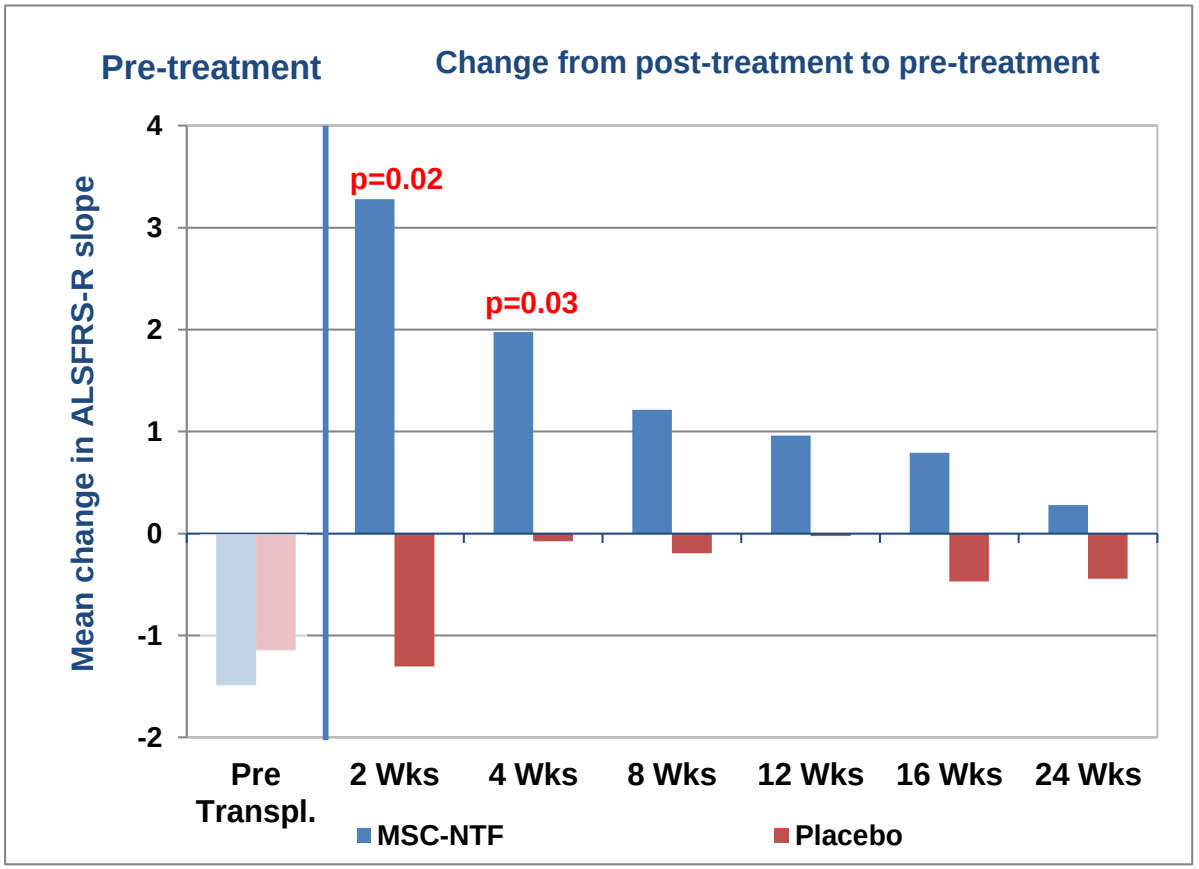
Ref Table: 14.2.11.4

ALSFRS-R Slope Improved Following Cell Therapy



Ref. Tables 14.2.1.1 14.2.1.4., 14.2.1.5, 14.2.1.6, 14.2.1.10, 14.2.1.11

Excluding slow progressors
Cell therapy produced more marked improvement of ALSFRS-R slope of decline



15 treated at all time-points. 5 placebo at weeks 2, 4 and 8 and 6 placebo at weeks 12, 16 and 24

Ref. Table 14.2.11.1.

Cerebrospinal Fluid (CSF) analyses

- Analyses of the CSF (to which the cells were injected) confirm the presence of the cells and their biological activity
- A significant increase in neurotrophic factors (secreted by the cells) and decrease in inflammatory factors, was observed post-transplant in the treated group only, providing a biological mechanism supporting the observed clinical effect

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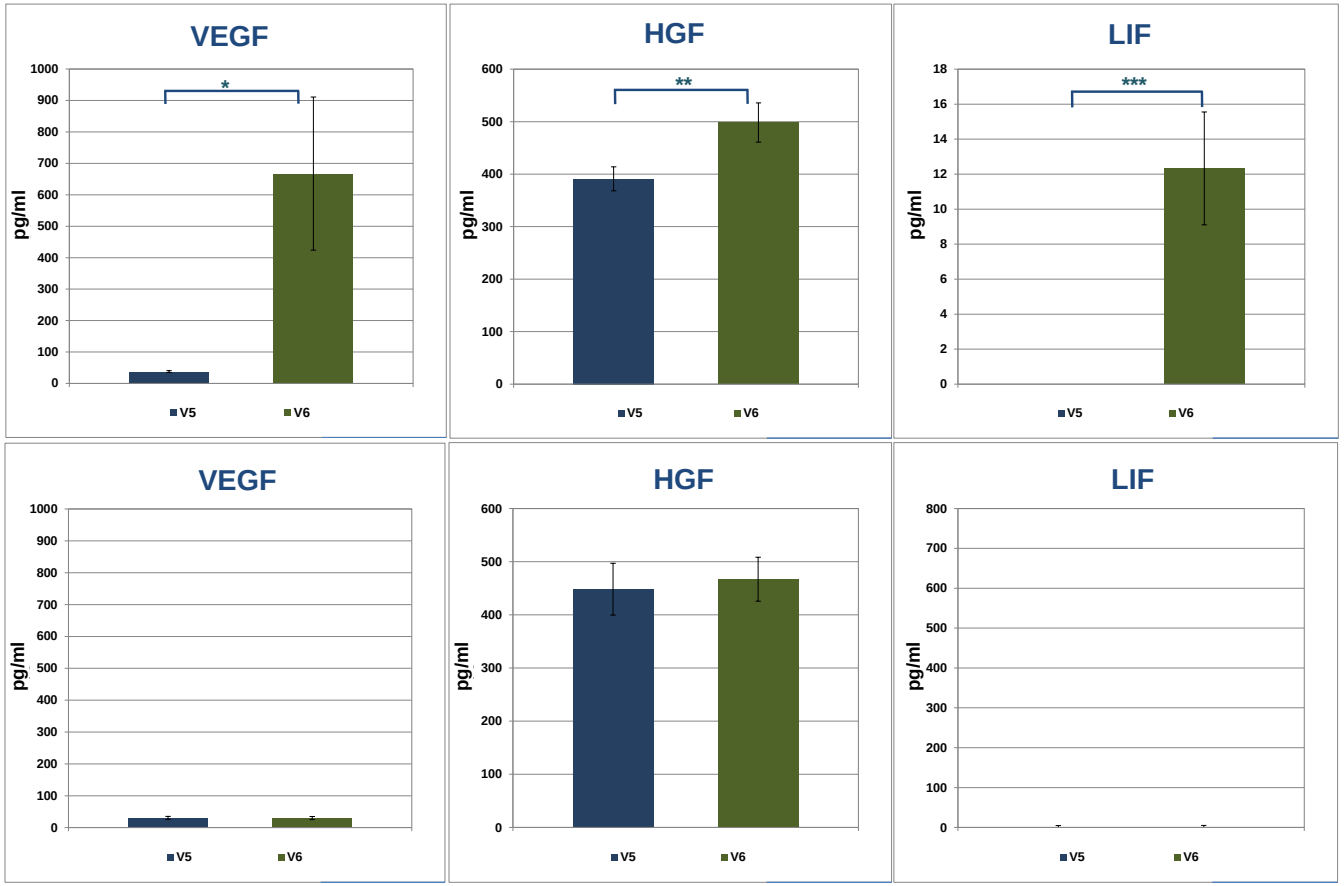
Cell therapy increased levels of neurotrophic factors in CSF

MSC-NTF n = 26

Placebo n = 9



Vascular endothelial growth factor (VEGF) induces endothelial cell growth and angiogenesis. In animal models of ALS, VEGF treatment leads to improvement of motor functions, protection of MNs and increase in survival

Hepatocyte growth factor (HGF) a growth factor acting on the liver has protective effects on Motor Neurons (MN) in vitro and in vivo. HGF was found to reduce MN degeneration and increase survival in rodent models of ALS.

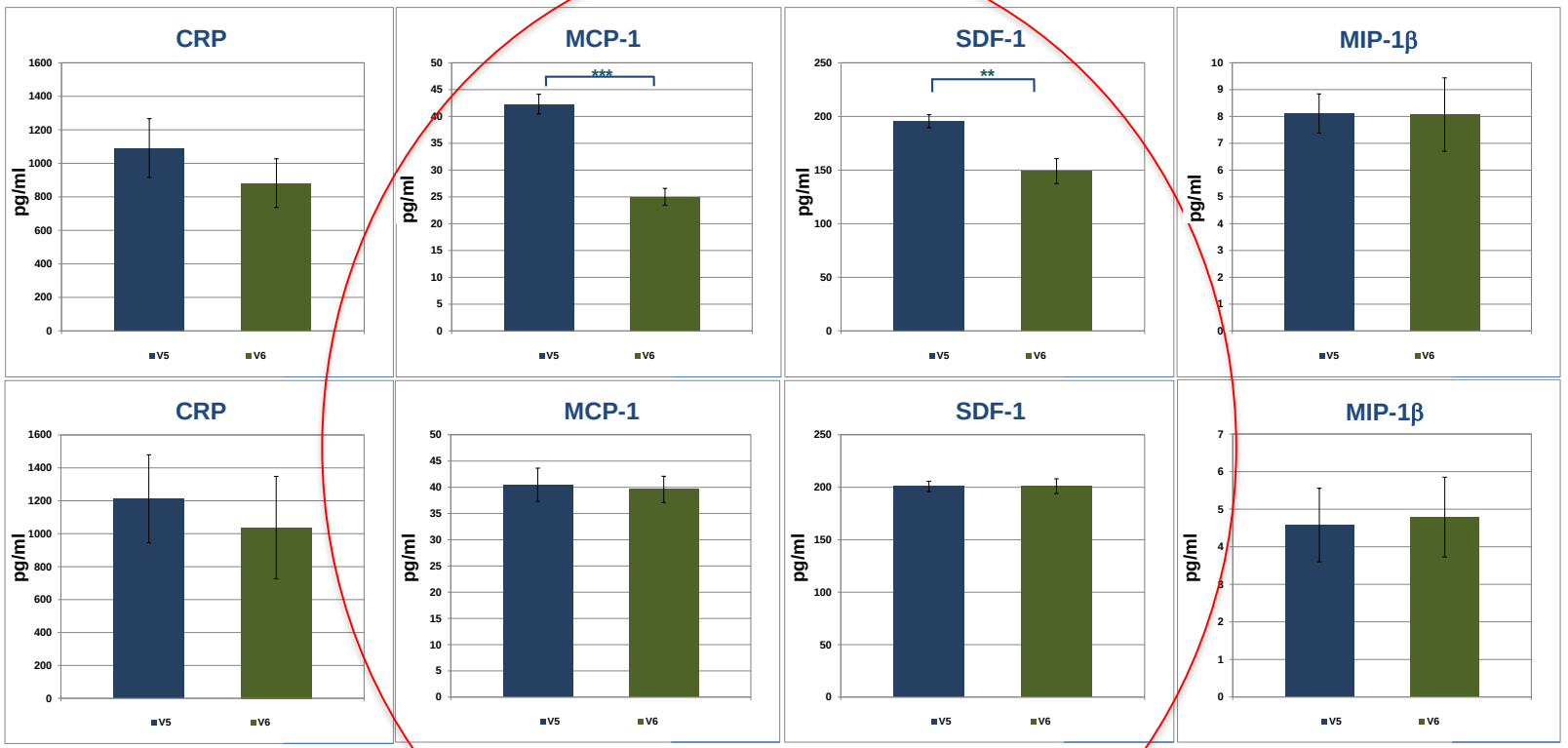
Leukemia inhibitory factor (LIF) is a multifunctional cytokine that exert different effects on different cell types. LIF was shown to support MN survival in-vitro and to reduce MN loss following nerve damage

Average ± SEM
* p< 0.05 ** p<0.01 *** p< 0.001

Cell therapy decreased some inflammatory markers in CSF

MSC-NTF n = 26

Placebo n = 9



C-reactive protein (CRP) is a liver produced protein widely used as an inflammation marker

Monocyte chemoattractant protein-1 (MCP-1), induces chemotaxis of macrophages and microglia, leading to pathological microgliosis and inflammatory activation

Stromal cell-derived factors 1- (SDF-1) is a small cytokine which activates leukocytes and microglia

Macrophage Inflammatory Proteins (MIP) belong to the family of chemotactic cytokines.

Average ± SEM ** p<0.01 *** p< 0.001

Conclusions

- Achieved primary objective - MSC-NTF cells safe and well tolerated.
- Related AEs almost exclusively mild/moderate:
  - Local discomfort and systemic reactions following transplant
- Clinical meaningful changes in ALSFRS-R
  - Statistically significant in pre-specified subgroup of rapid progressors
- Encouraging CSF biomarker profile (↑ NTF ↓ inflammatory markers).
- Next Step: Larger confirmatory trial with repeat dosing

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