NurOwn (MSC-NTF) Phase 2 Clinical Trial in Progressive MS: Effects on CSF Neuroprotective Biomarkers

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Conclusions

- In this phase 2 clinical trial, intrathecal MSC-NTF cell treatment resulted in robust increases in CSF neuroprotective biomarkers (VEGF, LIF, HGF, Follistatin, Fetuin-A, and NCAM1), consistent with the proposed mechanism of action.
- The neuroprotective biomarker data provide a biological context for the clinical outcomes observed in this study.
- These CSF biomarker observations may guide future efforts to optimize this innovative autologous mesenchymal cellular therapy in progressive MS.

Background

MSC-NTF cells (NurOwn®) are autologous bone-marrow derived mesenchymal stem cells (MSC) induced to secrete high levels of neurotrophic factors (NTFs) while maintaining their intrinsic immunomodulatory properties. CSF neuroprotective biomarkers such as vascular endothelial growth factor (VEGF)[1], hepatocyte growth factor (HGF)[2], and neural cell adhesion molecule 1 (NCAM-1)[3] have demonstrated a relationship to disease progression and treatment response in PMS. We analyzed the effects of MSC-NTF cell treatment on these and other key neuroprotective biomarkers in a phase 2 clinical trial.

Methods and Study Design

MSC-NTF cells were evaluated in a phase 2 clinical trial in progressive MS (NCT 03799718). Safety, consistent improvements in MS functional outcomes and biomarker results were reported. Eligible participants had baseline Expanded Disability Status Scale (EDSS) scores 3-6.5, had no clinical relapses within 6 months of study enrollment, and were able to walk 25 feet in 60 seconds or less. 18 participants received 100-125 x 10^6 intrathecal MSC-NTF cells by lumbar puncture at weeks 0, 8, and 16 and then were followed to week 28. CSF was collected at weeks 0, 8 and 16 (just prior to each treatment). Neuroprotective biomarkers (Leukemia Inhibitory Factor (LIF), VEGF, HGF, Follistatin, Fetuin-A, NCAM1, and Clusterin/ApoJ) were detected with a highly sensitive, customized ProcartaPlex multiplex immunoassay (Thermo Fisher Scientific, Waltham, MA). The assays were thoroughly validated by matrix evaluation including spike recovery, parallelism, and sample stability. Biomarker data were log transformed for analysis and percent changes were graphed in the original units. We present geometric means and the first (Q1) and third (Q3) quartiles.

Baseline Characteristics

Mean Age: Years (SD)	47 (9.6)
Females N(%)	10 (56 %)
EDSS Score: Mean (SD)	5.4 (1.3)
T25FW Score (ft/sec): Mean (SD)	2.4 (1.6)
9-HPT Score (sec) – Combined Average: Mean(SD)	35.2 (15.7)
MSWS-12 Score: Mean (SD)	75.6 (19.1)
LCLA Score – Binocular 2.5%: Mean (SD)	32.7 (8.9)
LCLA Score – Binocular 1.25%: Mean (SD)	23.3 (10.9)
SDMT Score: Mean (SD)	46.1 (11.5)
MSFC-4 Z score: Mean (SD)	0.03 (0.48)

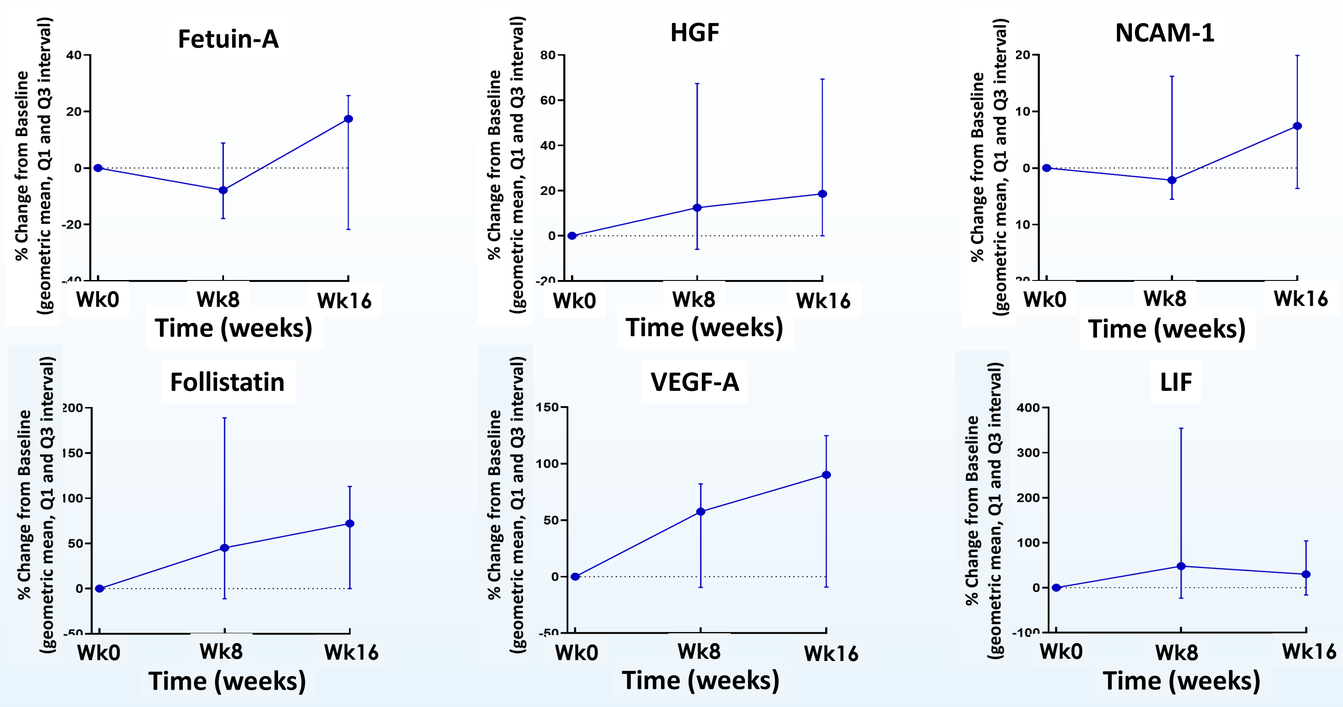
EDSS = expanded disability status scale; T25FW = timed 25-foot walk test; 9-HPT = 9-hole peg test; MSWS-12 = 2-item multiple sclerosis walking scale; LCLA Score = low contrast letter acuity; SDMT = symbol digit modalities test; MSFC-4 = multiple sclerosis functional composite.

Results - Primary Efficacy Endpoints

T25W OR 9-HPT (≥25% improvement)	3/16 (19%)
T25W (≥25% improvement)	2/14 (14%)
9-HPT (≥25% improvement), Combined Average	2/15 (13%)
LCLA binocular 1.25% (≥8 letter improvement)	7/15 (47%)
LCLA binocular 2.5% (≥8 letter improvement)	4/15 (27%)
SDMT (≥3 point improvement)	10/15 (67%)
SDMT (≥5 point improvement)	7/15 (47%)
EDSS (Baseline EDSS ≤ 5.5 with Improvement ≥ 1.0)	0/6 (0%)
EDSS (Baseline EDSS > 5.5 with Improvement ≥ 0.5)	3/10 (30%)
MSWS-12 (≥10-point improvement)	6/16 (38%)

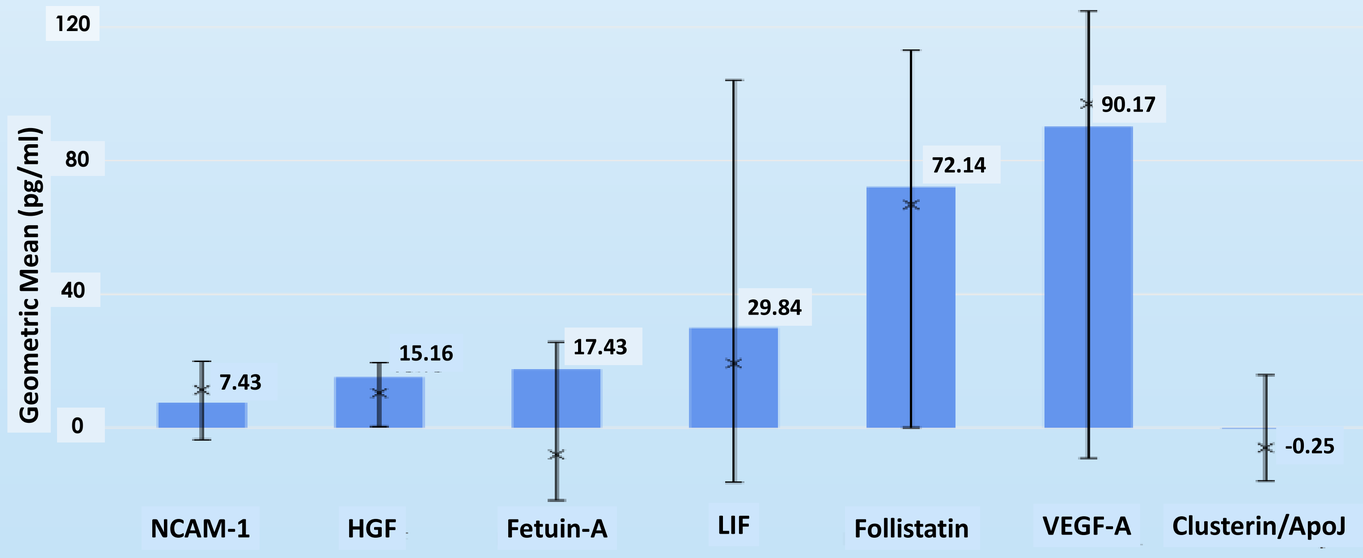
Responder Analyses (defined as prespecified threshold for clinical response of 25% or greater improvement) of efficacy endpoints over 28 weeks after three MSC-NTF cell intrathecal treatments in participants with progressive MS.

CSF Neuroprotective Biomarkers to Week 16



Presented as % change (geometric mean, Q1, Q3) at weeks 0, 8 and 16 just prior to intrathecal administration of MSC-NTF cells.

% Change in CSF Neuroprotective Biomarkers: Baseline to Week 16



Bars represent group means (% change from baseline); lines represent Q1 and Q3 quartiles; crosshairs represent group medians.

References

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Conflicts of Interest:

Dr. Jeffrey A Cohen reports personal compensation for consulting for Biogen, Bristol-Myers Squibb, Convelo, Genentech, Janssen, NervGen, Novartis, and PSI; speaking for H3 Communications; and serving as an Editor of *Multiple Sclerosis Journal.* .**Dr. Fred Lublin** reports research funding from: Novartis, Actelion, Biogen, Sanofi, NMSS, NIH, Brainstorm Cell Therapeutics; consulting agreements/advisory boards/DSMB activities with: Biogen, EMD Serono, Novartis, Teva, Actelion/Janssen, Sanofi/Genzyme, Acorda, Roche/Genentech, MedImmune/Viela Bio/Horizon Therapeutics, Receptos/Celgene/BMS, TG Therapeutics, Medday, Atara Biotherapeutics, Mapi Pharma, Apitope, Orion Biotechnology, Brainstorm Cell Therapeutics;, Jazz Pharmaceuticals, GW Pharma, Mylan, Immunic, Population Council, Avotres, Neurogene, Banner Life Sciences, Labcorp, Entelexo Biotherapeutics, Neuralight; stock Options from Avotres; and speaking for Sanofi (non-promotional). **Dr. Christopher Lock** reports personal compensation for speaking, advisory boards, or consulting for Biogen, Sanofi, EMD Serono, Alexion Pharmaceuticals, Bristol Myers Squib, Greenwich Biosciences, InterX Inc., and Diagnose Early. **Dr. Daniel Pelletier** reports consulting compensation for advisory board activities from Biogen, Sanofi/Genzyme, EMD Serono, and Roche/Genentech. **Dr. Tanuja Chitnis** reports personal compensation for consulting for Biogen, Novartis, Genentech, and Sanofi-Genzyme, and research funding from Brainstorm Cell Therapeutics, Novartis and Verily. **Dr. Munish Mehra** is an employee of Tigermed. **Dr. Yael Gothelf** is an employee of Brainstorm Cell Therapeutics. **Dr. Revital Aricha** is an employee of Brainstorm Cell Therapeutics. **Dr. Stacy Lindborg** is an employee of Brainstorm Cell Therapeutics. **Chaim Lebovits** is an employee of Brainstorm Cell Therapeutics. **Dr. Jenny Li** is an employee of Brainstorm Cell Therapeutics. **Dr. Sidney A Spector** is an employee of Brainstem Cell Therapeutics. **Dr. Ralph Kern** is an employee of Brainstorm Cell Therapeutics. **Dr. Kim Thacker** is an employee of Brainstorm Cell Therapeutics.