

Phase 2 Open-Label, Multicenter Study of Repeated Intrathecal Administration of Autologous MSC-NTF cells in Progressive Multiple Sclerosis

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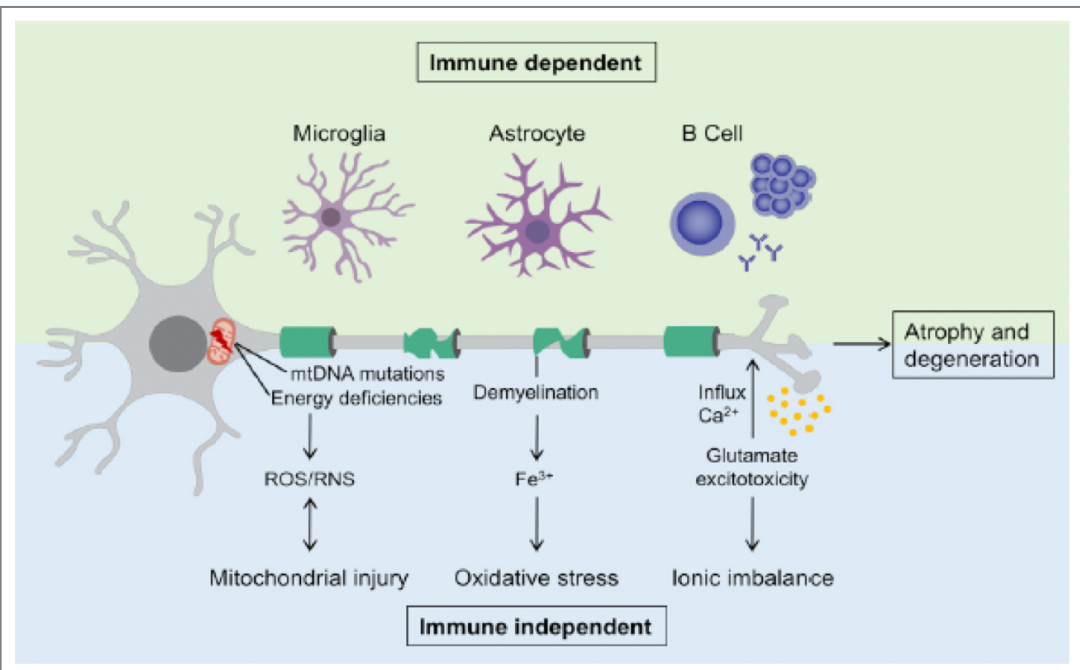


Background

Multiple Sclerosis (MS) is a chronic neuroinflammatory and neurodegenerative disorder of the central nervous system. Progressive MS is defined by the gradual accumulation of neurological disability independent of relapses, typically with lack of or incomplete recovery.¹

Therapies addressing regeneration and repair may offer an innovative treatment option in progressive MS.²

NurOwn® may impact both immune-dependent and independent processes in Progressive MS



Baecher-Allan et al, Neuron 2018

Autologous MSC-NTF cells are bone-marrow derived mesenchymal stem cells (MSCs) propagated and differentiated in culture to secrete high levels of neurotrophic factors.

In the experimental autoimmune encephalomyelitis mouse model, intracerebroventricular administration of autologous MSC-NTF cells were shown to delay the onset of motor impairment and improve survival.³

MSC-NTF cells are currently being evaluated in a 200 patient US phase 3 placebo-controlled, repeated intrathecal dose study in Amyotrophic Lateral Sclerosis (ALS).

NTF	Neuroprotection/Remyelination	Immunomodulation
HGF	Promotes oligodendrocyte development in EAE model and remyelination in non-immune CNS demyelination	Induces tolerogenic dendritic cells and Treg cells in EAE model
LIF	Increases myelin repair in EAE model; Induces OPC proliferation in vivo and following cuprizone demyelination; facilitates optic nerve regeneration via JAK/STAT in zebrafish model	Inhibits TH17 differentiation in EAE model; mediates MSC reduction of T cell proliferation in vitro and promotes Treg cells in vitro and in vivo
BDNF	Increases axonal survival and outgrowth in cultured hippocampal neurons; Increases myelination and myelin protein synthesis in EAE model; MSC-derived BDNF improved EAE outcomes	Down regulation of MHC class 2 molecules; mediate/augment effects of Copaxone in EAE model
VEGF	Increases motor neuron axonal survival in EAE model	Varied effects on BBB (i.e., VEGF alone in LPS model vs. MSC-secreted VEGF)

There is increasing recognition that NTFs delivered by autologous MSCs have the potential for immunomodulation, remyelination, and neuroprotection in Progressive MS.⁴

Study Design

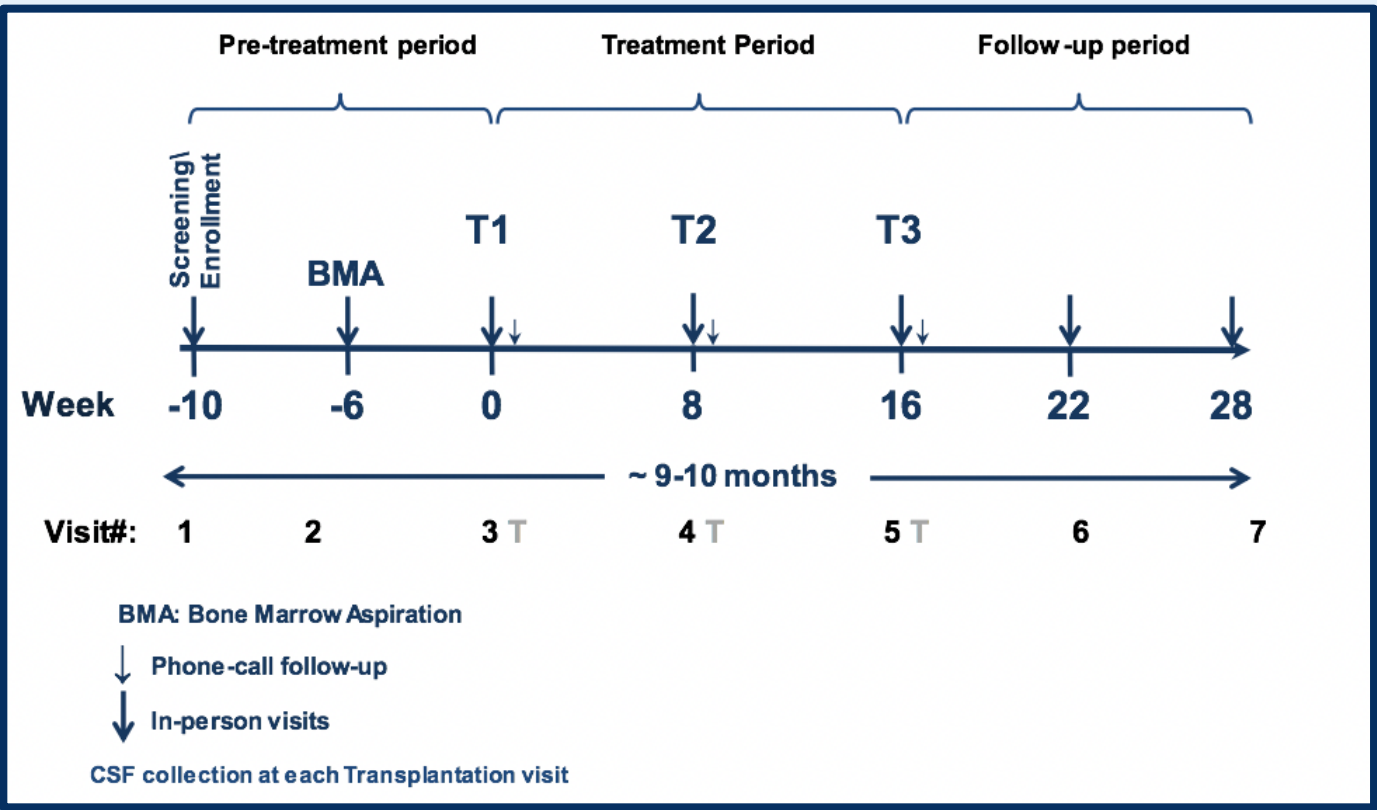
This open label, single-arm Phase 2 study, conducted at 5 US MS clinical centers, will evaluate the safety and efficacy of repeated doses of MSC-NTF cells using clinical outcome measures and paired CSF and blood biomarker analyses.

Study population: N=20 Progressive MS patients with Expanded Disability Status Scale (EDSS) 3.0-6.5, based on the 2017 revised McDonald Criteria.⁵

Inclusion Criteria

- ☐ Clinical diagnosis of Progressive MS (Primary and Secondary) based on the 2017 revised MacDonald Criteria; disease entered progressive stage for at least 6 months prior to enrollment
- ☐ No evidence of clinical MS relapse or corticosteroid treatment within 6 months prior to screening
- ☐ Disability status at screening with an Expanded Disability Status Scale (EDSS) is 3.0-6.5
- ☐ Able to walk 25 feet in 60 seconds or less
- ☐ Stable dose of non-excluded MS Disease Modifying Therapy for 6 months prior to screening visit

Eligible subjects will undergo a bone marrow aspiration (BMA) with the first IT transplantation ~ 6 weeks later. The next two transplantation visits occur 2 months apart with a 12 week follow-up period.



Study Duration:
9-10 months or 38 weeks
(10 weeks screening 16 weeks treatment, 12 weeks follow-up)

Enrollment Period:
4 months (March - June 2019)

FSFV-LSLV: 12 months
(March 2019 - February 2020)

Primary Endpoint:

- To evaluate safety and tolerability of 3 intrathecal doses of NurOwn®

Secondary Endpoints:

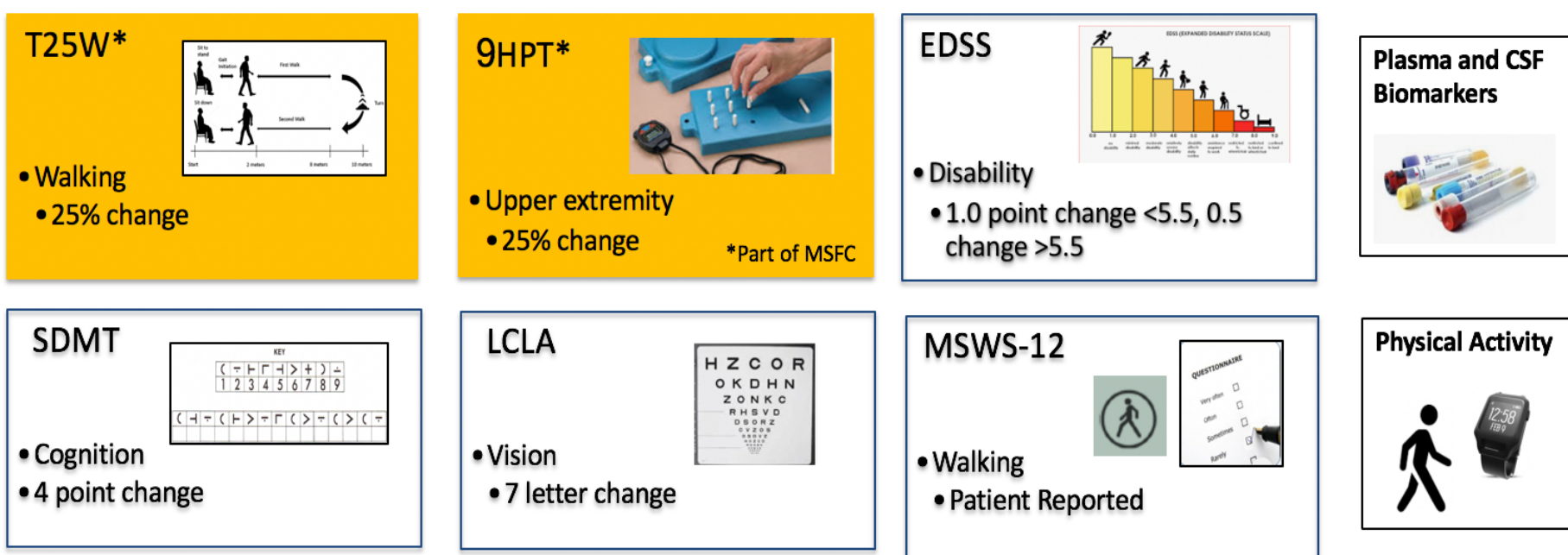
- To evaluate the efficacy of NurOwn® as measured by MS assessments
- To evaluate the modulation of CSF and blood biomarkers following NurOwn® transplantation

Safety Outcome Measures

- Changes in vitals and physical exam, safety labs, AEs, concomitant medications and MRI T1- and T2-weighted lesions
- Key safety data will be reviewed 1) when 50% of subjects have completed one treatment and 2) after all subjects complete the study

Efficacy Outcome Measures

- Timed 25 Foot Walk (T25FW), 9-Hole Peg Test (9HPT), Expanded Disability Status Scale (EDSS), Low Contrast Letter Acuity (LCLA) and Symbol Digital Modalities Test (SDMT)
- Biomarkers paired Blood plasma and CSF
- Physical function measured with wearable sensor and 12-item MS Walking Scale



Biomarkers: CSF and Blood Samples

- CSF and serum samples will be collected prior to each Transplantation of MSC-NTF cells.
- Samples will be evaluated for levels of disease and their potential relation to efficacy outcomes.

Biomarker Type	CSF	Serum
MSC-NTF derived Neurotrophic Factors	BDNF, GDNF, HGF, LIF, VEGF, TSG-6, G-CSF	BDNF, GDNF, HGF, LIF, VEGF, TSG-6, G-CSF
Inflammatory Biomarkers	MCP-1, SDF-1, CHIT-1, TNF- α , sCD27 and a full panel of cytokines, chemokines and regulatory proteins	Full panel of cytokines, chemokines and regulatory proteins
miRNA	miRNA panel	miRNA panel
Neurodegeneration	NfL, NfH, GFAP	NfL, NfH, GFAP

Study Status

Enrollment began in the first quarter of 2019 with topline clinical data expected in the first half of 2020.

Outcomes from a large contemporary, matched natural history cohort will be used in the data analysis.

Conclusion

This phase 2 open-label study was designed to provide preliminary data on the safety and efficacy of repeated intrathecal dosing of autologous MSC-NTF cells in progressive MS patients and will inform the design of a subsequent Phase 3 pivotal trial.

References

1. Lublin FD, et al. *Neurology* 2014. 2. Chataway J. Editorial. *Lancet Neurology* 2018. 3. Barhum Y, et al. *J Mol Neuroscience* 2010 4. Huang Y, et al. *Experimental Neurology* 2016 5. Thompson AJ, et al. *Lancet Neurology* 2017

Conflicts of Interest

Dr. Cohen reports personal compensation for consulting for Convelo and Gossamer Bio; speaking for Mylan; and serving as an Editor of *Multiple Sclerosis Journal*; Dr. Chitnis has served on advisory boards for Biogen, Novartis, and Sanofi-Genzyme; received research support from Biogen, Novartis, Octave, Serono and Verily; has participated in clinical trials sponsored by Sanofi-Genzyme and Novartis; Dr. Pelletier reports receiving consulting fees from Sanofi Genzyme, EMD Serono, Biogen, Novartis, Pear Therapeutics; Dr. Lock reports consulting fees for InterX Inc and Diagnose Early. Served as scientific advisory board member or speaker for Biogen, Sanofi Genzyme, and EMD Serono; Dr. Lublin reports sources of funding for research :Novartis; Actelion; Sanofi, NMSS and NIH. Consulting Agreements/Advisory Boards/DSMB fees: Biogen; EMD Serono; Teva; Actelion; Sanofi Genzyme; Acorda; Roche/Genentech; MedImmune; Receptos/Celgene; Forward Pharma; TG Therapeutics; Regeneron; Medday; Atara Biotherapeutics; Polpharma; Mapi Pharma; Innate Immunotherapeutics; Apitope; Orion Biotechnology; Brainstorm Cell Therapeutics; Jazz Pharmaceuticals; GW Pharma. Speaker fees for Sanofi (non-promotional).