MODULATION OF CSF CASPASE-3 IN MSC-NTF CELLS (NUROWN®) IN A PHASE 2 ALS STUDY: CORRELATIONS WITH CSF BIOMARKERS AND CLINICAL RESPONSE

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Phase 2 Study: CSF Biomarkers and Responder Analysis

Study Design n=48 (3:1 randomization)

Screening

BMA

IT/IM Transplantation

CSF Collection (V5 and V6)

Week 0

Week 2

-3 to -5 weeks

~3-4 months

-12 to -16 weeks

~ 6 months

12 weeks

24 weeks

End of Study

Week 0

CSF Collection

(~6 months)

Week 2

~3-4 months

BMA

Screening

Week 0

CSF Collection

 (~6 months)

Week 2

CSF Biomarkers:

↓MCP-1

↑miR-132

↓Caspase 3

Responder analysis: 100% ALSFRS-R slope improvement

**}* p < 0.001

Responder analysis: 100%

ALSFRS-R

slope improvement

Weeks

% Responders

MSC-NTF ALL

MSC-NTF RP

Placebo ALL

Placebo RP

Placebo SP

MSC-NTF SP

Weeks

8

12

16

20

24

28

% Responders

8

12

16

20

24

28

**}* p < 0.001
2X Greater CSF Caspase 3 % reduction in responders compared to non-responders at 12 weeks post-transplantation*

*** p< 0.001

*Responder defined as ≥100% ALSFRS-R slope improvement at 12 weeks
NurOwn® (MSC-NTF cells) may tip the balance linking neuronal cell death and neuroinflammation.

Neuronal apoptosis activates neuroinflammation via NFκ-B.
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Background

MSC-NTF cells (NurOwn®) are autologous bone-marrow derived mesenchymal stem cells (MSC) that secrete high levels of neurotrophic factors (NTFs) and immunomodulatory cytokines having a signature miRNAs profile. MSC-NTF cells were administered by the intrathecal (IT) route of administration to participants in a US Phase 2 ALS multicenter double-blind placebo-controlled trial to evaluate safety and efficacy (NCT02017912).

Objective

To measure CSF Caspase 3 levels pre- and post-single IT MSC-NTF cell transplantation and to correlate with clinical response and other CSF biomarkers.

Methods

CSF was collected prior to, and two weeks post-IT MSC-NTF cell transplantation. CSF Caspase-3, NTFs, cytokines and miRNAs were analyzed. Caspase-3 reduction was evaluated in responders (≥100% improvement in ALSFRS-R slope 12-weeks post transplantation) and non-responders. miR were analyzed in pooled CSF samples from responders, non-responders and placebo.

Results

Study Design n=48 (3:1 randomization)

Responder analysis: 100% ALSFRS-R slope improvement

The percentage of participants with a 100% improvement in their ALSFRS-R at the indicated time points in the treated (MSC-NTF) and the Placebo group total population (ALL), rapid progressors (RP) and slow progressors (SP).

Caspase-3 reduction was greater in responders compared to non-responders

Discussion

Decreased CSF Caspase-3 may reflect reduced neuronal apoptosis and serve as a biomarker for neuroprotection. While MSC-NTF cells may have anti-apoptotic effects through direct paracrine NTF mechanisms such as VEGF, it is possible that indirect effects may be mediated via immunomodulation and miR-132 secretion. Caspases are known to activate microglia via NF-kB signaling and miR-132 may regulate apoptotic genes. miR-132 appears to be lower in the CSF of sporadic ALS patients and TDP-43 is required for the biogenesis of miR-132. These findings support the combined immunomodulatory and neuroprotective mechanism of action of MSC-NTF cells through NTF, immunomodulatory and miRNA pathways.