Natalizumab Reduces Serum Concentrations of Neurofilament Light Chain in Secondary Progressive Multiple Sclerosis Patients From the Phase 3 ASCEND Study

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Objective:
To evaluate the associations of serum neurofilament light chain (sNfL) concentrations and disease activity, disability progression and response to natalizumab treatment in participants with secondary progressive multiple sclerosis (SPMS).

Background:
sNfL is a promising biomarker of disease activity and treatment response in relapsing-remitting multiple sclerosis (RRMS). The role of sNfL as a biomarker in SPMS is not well understood. ASCEND was a Phase 3 study of natalizumab in individuals with SPMS for ≥2 years.

Design/Methods:
sNfL concentrations were measured using SIMOA NF-light® Advantage Kit (Quanterix) at baseline, week 48, and week 96 in 748 participants (natalizumab/n=379, placebo/n=365) from ASCEND. Statistical analyses included Spearman correlation, mixed model for repeated measure, and ANCOVA.

Results:
Baseline sNfL concentrations were associated ($p<0.0001$) with number of Gd+ lesions, T2 lesion volume, Timed 25-Foot Walk time (T25FW), 9-Hole Peg Test time (9HPT) at baseline, and brain atrophy over 96 weeks. At week 96, sNfL concentrations were significantly higher in participants with progression [defined using EDSS ($p<0.01$), T25FW ($p<0.05$), or 9HPT ($p<0.01$)], compared to those without progression during the study. sNfL concentrations at weeks 48 and 96 were significantly lower in natalizumab versus placebo participants (ratio 0.84/95% CI [0.79, 0.89], $p<0.001$ and ratio 0.80/95% CI [0.7, 0.85], $p<0.001$, respectively); statistically significant sNfL differences were observed in participants with and without Gd+ lesions at baseline, relapses in 2 years before study enrollment and inflammatory activity (Gd+ lesions, new T2 lesions or relapse) during the study. Data on natalizumab response stratified by NfL concentrations will be presented.

Conclusions:
Similar to observations in RRMS, baseline sNfL in SPMS participants was associated with baseline disease activity measures and future brain atrophy rates. Natalizumab reduced sNfL versus placebo in SPMS participants with/without acute inflammation. These findings suggest that sNfL may reflect both acute inflammation-driven neuro-axonal damage and chronic neurodegeneration in MS.