Natalizumab Reduced Serum Levels of Neurofilament Light Chain in Secondary Progressive Multiple Sclerosis Patients from the Phase 3 ASCEND Study

Kapoor R.1, Seeliger F.2, Hartung HP.2, Arnold DL.1, Freedman MS.1, Jeffrey D.3, Miller A.2, Edwards KR.2, Singh CM.2, Chang L.1, Ren Z.2, Sangurdak D.1, Zhu B.1, Sheikh S.1, Mehta D.1, Ho P.R.1, Campbell N.1, Edwards M.1, Fisher E.2, Kieseier BC.3, Rudick RA.4, Plasina T.5

1UC Institute of Neurology, London, UK; 2Danish Multiple Sclerosis Center, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; 3Department of Neurology, Medical Faculty, Heinrich-Heine University, Düsseldorf, Germany; 4Montreal Neurological Institute, McGill University, Montreal, QC, Canada; 5University of Ottawa, Ottawa Hospital Research Institute, Ottawa, ON, Canada; 6Pediatric HealthCare, Monroe NC, USA; 7Icahn School of Medicine at Mount Sinai, New York, NY, USA; 8NMS Center of Northeastern New York, Lakham, NY, USA; 9Brigham, Cambridge, MA, USA

**Conclusions**

- Similar to previous observations in patients with RRMS, baseline sNfL concentrations in patients with SPMS in the ASCEND study were associated with baseline disease activity measures and future brain atrophy rates over a 96-week period.
- Natalizumab reduced sNfL concentrations compared to placebo in patients with SPMS with or without acute inflammatory activity.
- Our findings suggest that sNfL might not only reflect inflammation-driven neuroaxonal damage, but also non-inflammatory neurodegeneration in patients with MS.
- Further studies are needed to corroborate our observations.

**Introduction**

- Serum neurofilament light chain (sNfL) is a promising biomarker of disease activity and treatment response in individuals with relapsing-remitting multiple sclerosis (RRMS).1
- Data supporting the use of sNfL in individuals with secondary progressive multiple sclerosis (SPMS) are comparatively scant.
- The ASCEND study was a Phase 3 study in individuals with SPMS for ≥2 years.2

**Objectives**

- To evaluate the associations of sNfL and disease activity, disability progression, and response to natalizumab treatment in patients with SPMS enrolled in the ASCEND study.

**Methods**

- ASCEND Part 1 was a randomised, double-blind, parallel group, placebo-controlled, multicentre study (Figure 1.3)
  - Participants aged 18–58 years, with Expanded Disability Status Scale (EDSS) score 3.0–6.5, Multiple Sclerosis Severity Score ≤4 and disability progression not related to clinical relapses in the year before enrolment, received natalizumab or placebo for up to 96 weeks.
  - sNfL concentrations were measured at baseline, Week 48 and Week 96 and were available in 744 patients, 379 randomised to natalizumab and 305 randomised to placebo. Magnetic resonance imaging was done at baseline and every 24 weeks until Week 96.

**Results**

- Demographic and clinical characteristics of participants in ASCEND with sNfL concentrations are presented in Table 1.
- Baseline sNfL concentrations were significantly associated with number of gadolinium-enhancing (Gd+) lesions (P = 0.001), T2 lesion volume (P = 0.001), Timed 25-Foot Walk (T25FW) time (P = 0.001), Intrinsic Peg Test (IPT) time (P = 0.001) at baseline and brain atrophy over 24 weeks (P = 0.002, Table 2).
- At Week 96, Gd+ concentrations were significantly higher in patients with progression compared to those without progression during the study: progression was defined using EDSS (Figure 2A, P = 0.01), T25FW (Figure 2B, P = 0.02) or IPT (Figure 2C, P = 0.02; Figure 2D, Weeks 48-P = 0.03; and 96 (P = 0.02).
- At Weeks 48 and 96, sNfL concentrations were significantly lower in natalizumab-treated patients compared to those on placebo, respectively, 0.84% (95% CI, 0.70–0.98; P = 0.003) vs. ratio, 0.80 (95% CI, 0.75–0.85; P = 0.001; Figure 3A).
- Statistically significant differences in sNfL concentrations between the natalizumab and placebo groups were observed in patients with and without (Figure 3C) Gd+ lesions at baseline, relapses in the 2 years before study enrolment (Figure 3D) and inflammatory activity (Gd+ lesions, new T2 lesions or MS relapse [adjudicated] during the study; Figure 3E-G).

**References**