Effect of Siponimod on Cognition in Patients with Secondary Progressive Multiple Sclerosis (SPMS): Phase 3 EXPAND Study Subgroup Analysis
Ralph Benedict1, Robert Fox2, Davorka Tomic3, Bruce Cree4, Patrick Vermersch5, Gavin Giovannoni6, Amit Bar-Or7, Ralf Gold8, Shannon Ritter3, Goeril Karlsson3, Christian Wolf9, Ludwig Kappos10
1University At Buffalo, 2Cleveland Clinic, 3Novartis Pharma AG, 4UCSF, Multiple Sclerosis Center, 5CHR de Lille, 6QMUL, 7University of Pennsylvania, 8Neurologische Universitaetsklinik, 9Lycalis Sprl, 10Neurology, University Hospital Basel

Objective: To evaluate the effects of siponimod on cognitive processing speed (CPS) in SPMS using the Symbol Digit Modalities Test (SDMT).

Background: Cognitive impairment affects 50–70% of MS patients and is more severe in progressive than relapsing course. CPS is the most frequently affected cognitive domain; SDMT is the recommended gold standard measure of CPS. We previously reported a benefit of siponimod on CPS; here, we explore whether this benefit was affected by the CPS status at baseline.

Design/Methods: SPMS patients receiving siponimod (N=1099) or placebo (N=546) in the EXPAND study underwent SDMT at baseline and at 6-monthly intervals. A mixed-model repeated measures determined statistically significant group effects and a Cox proportional hazards model determined if these effects were clinically meaningful. "Sustained" change was defined as change from baseline by ≥4 points sustained on all subsequent assessments. Subgroup analyses were performed for patients with or without cognitive impairment at baseline (impaired SDMT <43; Drake et al 2018), and with a baseline SDMT ≥median or <median.

Results: The proportion of patients with sustained improvement in SDMT was greater for siponimod versus placebo for patients with or without cognitive impairment at baseline, reaching significance for those without impairment (HR 1.49 [1.09,2.04]; p=0.0126), and for those with baseline SDMT ≥median and <median, reaching significance for those with baseline SDMT ≥median (HR 1.46 [1.10,1.95]; p=0.0094). Also, the proportion of patients with sustained deterioration was less with siponimod versus placebo for those with or without cognitive impairment, reaching significance for both groups: HR 0.72 ([0.53,0.96]; p=0.0269) and HR 0.76 ([0.58,1.00]; p=0.0477), respectively, and among those with baseline SDMT <median and ≥median, reaching significance for those with baseline SDMT <median (HR 0.65 [0.47,0.89]; p=0.0071).

Conclusions: Siponimod demonstrated significant functional benefits on CPS in SPMS patients, both for sustained improvement and against sustained deterioration in SDMT.