Effect of siponimod on cognitive processing speed in SPMS patients with active and non-active disease

Background
Siponimod significantly reduced the relative risk of 3-month (m) confirmed disability progression (CDP) by 21% and 6mCDP by 26% versus placebo in the EXPAND core study. Siponimod also showed a significant benefit on cognitive processing speed (CPS) as measured by change in the Symbol Digit Modalities Test (SDMT).

Objectives
To evaluate the effect of siponimod on CPS in subgroups of patients with active (aSPMS) and non-active (naSPMS) disease from the EXPAND core study.

Methods
EXPAND (N=1651) was a double-blind Phase 3 study that randomized a broad range of SPMS patients to siponimod or placebo (2:1). This subgroup post-hoc analysis included patients with aSPMS (siponimod, n=516; placebo, n=263; defined as presence of relapses in the 2 years before screening and/or ≥1 TI gadolinium-enhancing lesions at baseline) and naSPMS (siponimod, n=557; placebo, n=270; counterpart of aSPMS). The outcomes analyzed were change in SDMT score from baseline to M24 derived from the mixed model for repeated measures; time to 6m confirmed ≥4-points cognitive worsening/improvement (6mCW/6mCI) on SDMT and a categorical analysis showing the proportion of patients with worsened, stable and improved SDMT scores (worsened/improved by ≥4 points since baseline and until the end of the trial, or otherwise stable) at M24.

Results
Change in SDMT (95% CI) versus placebo from baseline to M24 in the aSPMS and naSPMS groups was 2.34 (0.66; 4.02) and 2.44 (0.67; 4.22; p<0.01 for both), respectively, consistent with the overall EXPAND core population (2.28 [1.09; 3.48]; p<0.001). In patients with aSPMS, siponimod reduced the risk of 6mCW by 27% (hazard ratio [95% CI]: 0.73 [0.53; 1.03]; p=0.06) and improved the chance of 6mCI by 62% (1.62 [1.14; 2.29]; p=0.007) versus placebo. Corresponding values in the naSPMS group were: 6mCW, 24% (0.76 [0.53; 1.09]; p=ns) and 6mCI, 19% (1.19 [0.86; 1.65]; p=ns). In the aSPMS group, a lower proportion of patients worsened (27.3% vs 38.2%, p=0.002) and a higher proportion of patients improved (34.1% vs 22.9%, p=0.001) on SDMT versus placebo. Corresponding proportions for the naSPMS group were: worsened, 21.2% vs 23.7%, p=ns; improved, 35.6 vs 31.2%, p=ns.

Conclusions
Siponimod was associated with relevant benefits in CPS as measured by change in SDMT in patients with active and non-active SPMS. In patients with active disease, both a reduced risk for clinically relevant worsening and an increased chance for clinically relevant improvement were observed.