Abstract 1588

Impact of siponimod on myelination as assessed by MTR across SPMS subgroups: Post-hoc analysis from the EXPAND MRI substudy

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Background

Changes in magnetization transfer ratio (MTR) are a marker of changes in myelin density and associated tissue integrity in the brain. Siponimod improved MTR recovery in lesions and demonstrated a significant effect on MTR decrease in normal-appearing brain tissue (NABT) and cortical grey matter (cGM) with a more pronounced effect on normal-appearing white matter (NAWM) in the overall EXPAND secondary progressive multiple sclerosis (SPMS) population, as reported previously.

Objectives

To investigate the effect of siponimod vs placebo (PBO) on MTR changes in NABT, cGM, and NAWM in subgroups of SPMS patients.

Methods

This prospective MTR substudy assessed the effect of siponimod versus PBO on median normalized MTR (nMTR) in NABT, cGM and NAWM assessed by absolute change from baseline (BL) to Month (M) 24 using repeated measures models. Patient subgroups were defined by: **disease history and severity** (age [≤45/>45 years], disease duration [≤15/>15 years], Expanded Disability Status Scale (EDSS) score [≤5.5/≥6.0], Symbol Digit Modalities Test score (≤43/>43); and **inflammatory disease activity** (active/non-active SPMS, with/without relapse in 2 years before screening, with/without gadolinium-enhancing lesions). Data from the per-protocol set (n=443) are presented.

Results

The subgroup analysis indicated that absolute changes from BL in median nMTR for NAWM ranged from –0.124 to –0.034 in the PBO group and from –0.016 to 0.040 in the siponimod group, which corresponds to 79–198% attenuation in median nMTR decrease versus PBO across all the subgroups studied (all p<0.05 except EDSS≥6 subgroup, p=0.064). The results were consistent for NABT (70–170%) and cGM (44–188%) although slightly less pronounced (p>0.05 for some subgroups). In the active SPMS subgroup, siponimod attenuated median nMTR decrease across NABT, cGM and NAWM by 91–109% (p<0.01 all); and in the non-active SPMS subgroup by 170–198% (p=0.0151 for NAWM, p>0.05 for NABT, cGM).

Conclusions

Over 24 months, siponimod attenuated the decrease in median nMTR in brain tissues across the patient subgroups characterized by disease activity and severity. The effect of siponimod was most pronounced in NAWM. These data support preclinical studies of siponimod, showing direct beneficial CNS effects on myelination.

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