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

Type: Oral Presentation

Keyword: Imaging

Authors: D.L. Arnold¹, A. Bar-Or², B.A.C. Cree³, G. Giovannoni⁴, R. Gold⁵, P. Vermersch⁶, D. Piani-Meier⁷, T. Hach⁷, S. Arnould⁷, G. Karlsson⁸, L. Kappos⁹, R.J. Fox⁹, ¹NeuroRx Research/Montreal, QC/Canada, ²Center for Neuroinflammation and Experimental Therapeutics and Department of Neurology, Perelman School of Medicine, University of Pennsylvania/Philadelphia, PA/United States of America, ³UCSF Weill Institute for Neurosciences, Department of Neurology, University of California San Francisco/San Francisco, CA/United States of America, ⁴Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London/London/United Kingdom, ⁵Department of Neurology, St Josef-Hospital/Ruhr-University Bochum/Bochum/Germany, ⁶Univ. Lille, Inserm U1172, CHU Lille, FHU Imminent/Lille/France, ⁷Novartis Pharma AG/Basel/Switzerland, ⁸Neurologic Clinic and Policlinic, Departments of Medicine, Clinical Research, Biomedicine and Biomedical Engineering, University Hospital, University of Basel/Basel/Switzerland, ⁹Mellen Center for Treatment and Research in Multiple Sclerosis, Neurological Institute/Cleveland, OH/United States of America

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.