Innovative Comparative Study Assessing the Effect of Siponimod on Reactive Microglia/Astrocytes in Patients With Secondary Progressive Multiple Sclerosis: Study Design

Robert Zivadinov[1,2,3], Bianca Weinstock-Guttman[2], Ralph Benedict[2], Michael G. Dwyer[1,2,3], Ferdinand Schweser[1,2,3], Dejan Jakimovski[1], Niels Bergsland[1,2], Daniela Piani-Meier[4], Harald Kropshofer[4]
[1]Buffalo Neuroimaging Analysis Center, Buffalo, NY, USA, [2]Department of Neurology, University at Buffalo, Buffalo, NY, USA, [3]Center for Biomedical Imaging, Clinical and Translational Science Institute, University at Buffalo, Buffalo, NY, USA, [4]Novartis Pharma AG, Basel, Switzerland

Objective:
To assess the effect of siponimod, compared to ocrelizumab, on reactive microglia/astrocytes using positron emission tomography (PET) and magnetic resonance imaging (MRI) in patients with active secondary progressive multiple sclerosis (aSPMS).

Background:
Chronic activation of microglia/astrocytes drives central inflammation, neurodegeneration, and demyelination leading to gray matter (GM) and white matter (WM) damage in MS. Activated microglia/astrocytes form clusters detectable by targeting an 18-kilodalton translocator protein (TSPO) using [F18]-PBR06-PET. Preclinical evidence suggests siponimod can shift microglia/astrocytes to a pro-repair phenotype and promote re-myelination. Clinical evidence from the EXPAND study demonstrated favourable siponimod effects on GM atrophy (neurodegeneration) and magnetization transfer ratio (myelin content), in line with pre-clinical findings.

Design/Methods:
An open-label, single-blinded (MRI analysis), observational, comparative, prospective, 36-month, adaptive study will be conducted in aSPMS patients (aged 18–60 years with evidence of clinical and/or MRI disease activity [Lublin 2014 Criteria] and EDSS of 3.0 to 6.5). Following enrollment of each SPMS patient starting siponimod treatment, a matching (ratio 1:1) of SPMS patient starting ocrelizumab treatment will be enrolled. PET, MRI, serum biomarker, and clinical and cognitive assessments will be conducted at 0, 6, 12, 24 and 36 months.

Results:
The study plans to enroll 60 patients with aSPMS who are treatment-naïve to siponimod/ocrelizumab. The primary endpoint is change from baseline in PET-activation of PBR06 in lesional/non-lesional normal appearing (NA) WM, NAGM, and peri-plaque area of chronic lesions. Secondary endpoints include change in PET-activation of PBR06 in these areas between siponimod and ocrelizumab groups, and cumulative number of ultra-small superparamagnetic particle iron oxide-positive lesions on MRI between two treatment arms. First and second interim analyses are planned after 50% and 100% of ongoing patients have reached month 12. The first-patient-first-visit is scheduled in October 2021.

Conclusions:
This is the first and largest PET/MRI imaging/bio-signature study in MS evaluating siponimod's effect on microglia/astrocyte activation compared with ocrelizumab.