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

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Disclosures

Robert Zivadinov has received personal compensation from Bristol Myers Squibb, EMD Serono, Sanofi, Keystone Heart, Protembis and Novartis for speaking and consultant fees. He received financial support for research activities from Sanofi, Novartis, Bristol Myers Squibb, Octave, Mapi Pharma, Keystone Heart, Protembis and V-WAVE Medical

Bianca Weinstock-Guttman has received honoraria as a speaker and/or as a consultant for Biogen Idec, Sanofi &Genzyme, Genentech, Novartis , BMS, Bayer, Horizon and Janssen. Dr Weinstock-Guttman received research funds from Biogen Idec, Genentech and Novartis.

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Introduction

- TSPO is considered a PET imaging marker of brain-resident micro-/astroglia and myeloid cells that have invaded the brain[1]
- Over 95% of TSPO+ cells in PET scans are macrophages and microglia. Both homeostatic and pro-inflammatory, denoted as “reactive,” microglia cells express the same levels of TSPO[1]
- The apparent signal increase in TSPO+ cells in PET of MS as compared to healthy brains is due to formation of clusters of reactive microglial cells and macrophages in chronic active paramagnetic lesion rims, slowly evolving lesions, and in NAWM and NAGM. Thus, TSPO-PET elucidates the ultrastructural hallmarks of progressive MS
- USPIO* i.v. can be potentially used to differentiate between TSPO+ microglia/macrophages: it is phagocytosed by myeloid cells in the periphery and serves as a biomarker of invaded TSPO+ macrophages or resident TSPO+ microglia
- Astroglia contributes weakly (<5%) to TSPO+ cells and is mainly found in inactive lesions and in the center of active lesions, both considered less relevant for progression[1]
- In the SPMS phase III (EXPAND) study, siponimod effects on GM atrophy (neurodegeneration) and magnetization transfer ratio (myelin content) have been shown[2]

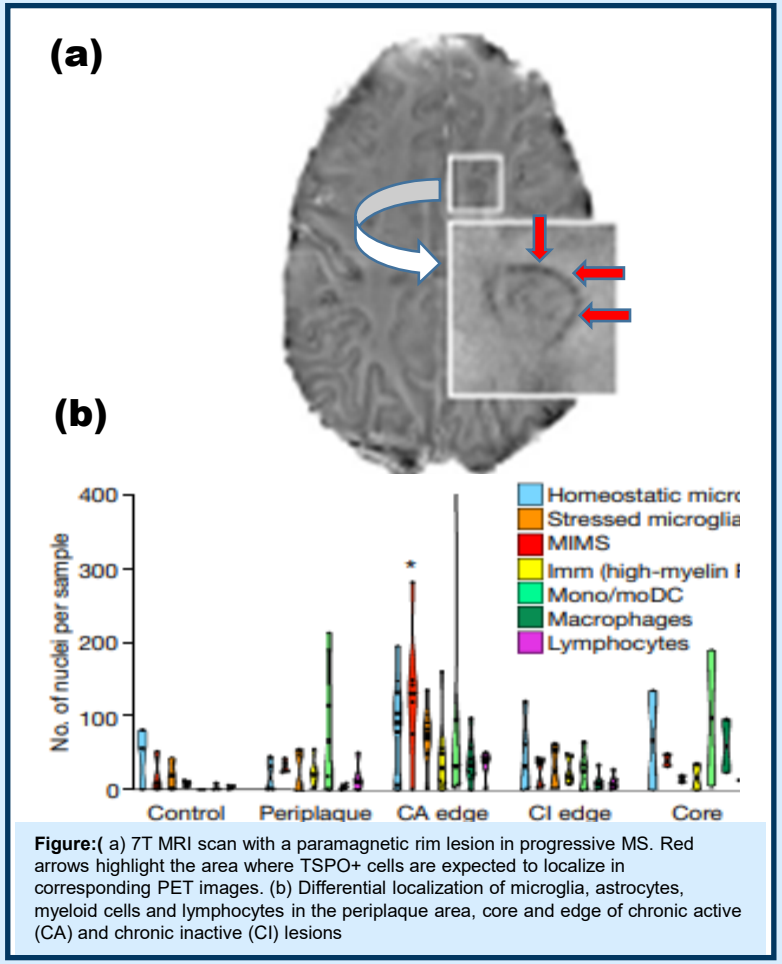

Figure:(a) 7T MRI scan with a paramagnetic rim lesion in progressive MS. Red arrows highlight the area where TSPO+ cells are expected to localize in corresponding PET images. (b) Differential localization of microglia, astrocytes, myeloid cells and lymphocytes in the periplaque area, core and edge of chronic active (CA) and chronic inactive (CI) lesions

*This is ultrasmall paramagnetic iron which is taken up by monocytes in the periphery and later shows up in the brain and can be detected in iron-enriched lesion rims, overlapping, in part, with the location of the TSPO PET signal in active SPMS patients.
GM, gray matter; i.v, intravenous; MS, multiple sclerosis; NAGM, normal-appearing gray matter; NAWM, normal-appearing white matte; PET, positron emission tomography; SPMS, secondary progressive multiple sclerosis; TSPO, translocator protein; USPIO, ultrasmall superparamagnetic iron oxide particles
1 Nutma E, et al.*Glia I: 10.1002/*.24052; 2. Bigaud M, et al .presented at AAN 2021.

Objective & Study Design

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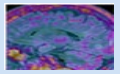
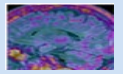
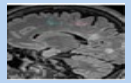
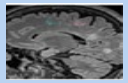
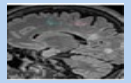
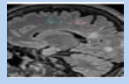
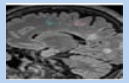
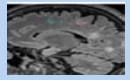
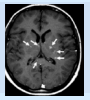
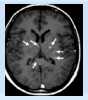
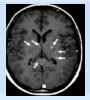
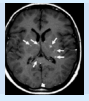
To assess the effect of siponimod, compared to ocrelizumab, on reactive microglia/astrocytes using PET, MRI and serum biomarkers NfL and GFAP in patients with active SPMS

An open-label, single-blind (MRI analysis), comparative, prospective, 36-month adaptive study

Number of patients: 60 (30- Siponimod; 30- Ocrelizumab)

Timelines	Baseline	6 Month	12 Month	24 months	36 months	EOT	
PET							^{18}F-PBR06
MRI							New T2 and Gd+T1 lesions
MRI (Gd+ & USPIO+)							USPIO+ lesions
Blood Samples							NfL, GFAP, SOMAScan
Neuro Exam							EDSS, SDMT (BICAMS), 9-HPT, T25FWT, relapses
Safety assessments							Adverse events

BICAMS, Brief International Cognitive Assessment for MS; EDSS, Expanded Disability Status Scale; EOT, end of treatment; Gd, gadolinium; GFAP, glial fibrillary acidic protein; MRI, magnetic resonance imaging; NfL, neurofilament light; PBR, Peripheral benzodiazepine receptor; PET, positron emission tomography; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis; T25FW, Timed 25-foot Walk; USPIO, ultrasmall superparamagnetic iron oxide particles

Eligibility Criteria

Key inclusion criteria

- Diagnosed with aSPMS (Lublin criteria[1])
- Age 18 to 60 years
- EDSS 3.0 to 6.5
- Treatment naïve to both siponimod and to ocrelizumab
- Not using S1P modulators or B-cell therapies for the last 9 months
- Creatinine clearance >59
- No known hypersensitivity reactions to contrast agent

Key exclusion criteria

- Treatment within 30 days prior to enrollment with steroids or any other concomitant immunomodulatory therapies
- LAB for the DNA single nucleotide polymorphism of the TSPO gene on chromosome 22q13.2, using a TaqMan assay
- A CYP2C9*3/*3 genotype
- Presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome
- Conditions associated with iron overload
- Women who are pregnant, lactating or of childbearing age

aSPMS, active secondary progressive multiple sclerosis; AV, atrioventricular; DNA; deoxy ribonucleic acid; EDSS, Expanded Disability Status Scale; LAB, blood test for low affinity; TSPO, translocator protein; WM, white matter

1. Lublin FD, et al. Neurology. 2014;83(3):278-286.

Endpoints

Primary

- Change from baseline in PET activation of PBR06 (when 100% of the patients have reached Month 12) in
  - Lesional and peri-lesional chronic WM areas in the brain, identified as gadolinium non-enhancing hyperintense T2 and hypointense T1 PRL+ and PRL- on QSM

Secondary

- Change in PET activation of PBR06 between siponimod and ocrelizumab at 6, 12, 24, and 36 months from baseline in
  - Non-lesional normal-appearing white and gray matter
- Cumulative number of USPIO lesions, Gd+ active lesions on T1-weighted images

Exploratory/tertiary

- Slowly expanding lesions
- Association between PET ^{18}F-PBR06 in lesional and non-lesional NAWM and NAGM and in the periplaque area of chronic lesions at 12, 24 and 36 months and
  - Cumulative number of new USPIO+ active lesions
  - Cumulative number of new Gd+ active lesions
  - PBVC, PCVC, and PTVC
- QSM changes in the thalamus and periplaque area of chronic lesions in the brain
- Association between imaging and clinical outcomes including the composite EDSS+SDMT
- Association of sNfL, GFAP, OCT and LCLA with TSPO PET and clinical outcomes

CE, contrast enhancing; GFAP, glial fibrillary acidic protein; LCLA, low contrast letter acuity; NAGM, normal appearing gray matter; NAWM, normal appearing white matter; OCT, optical coherence tomography; PBVC, percent brain volume change; PCVC, percent cortical volume change; PET, positron emission tomography; PRL, paramagnetic rim lesion; PTVC, percent thalamic volume change; QSM, quantitative susceptibility mapping; USPIO, ultrasmall superparamagnetic iron oxide particles

Preliminary Results

- The study started enrollment in November 2021
- We are expecting completion of enrollment by June 2023 and completion of follow-up by June 2026
- A first interim analysis will be conducted after 50% of the patients have reached Month 12
- A second interim analysis will be conducted after 100% of the patients have reached Month 12 and 50% of the patients have reached 24 month

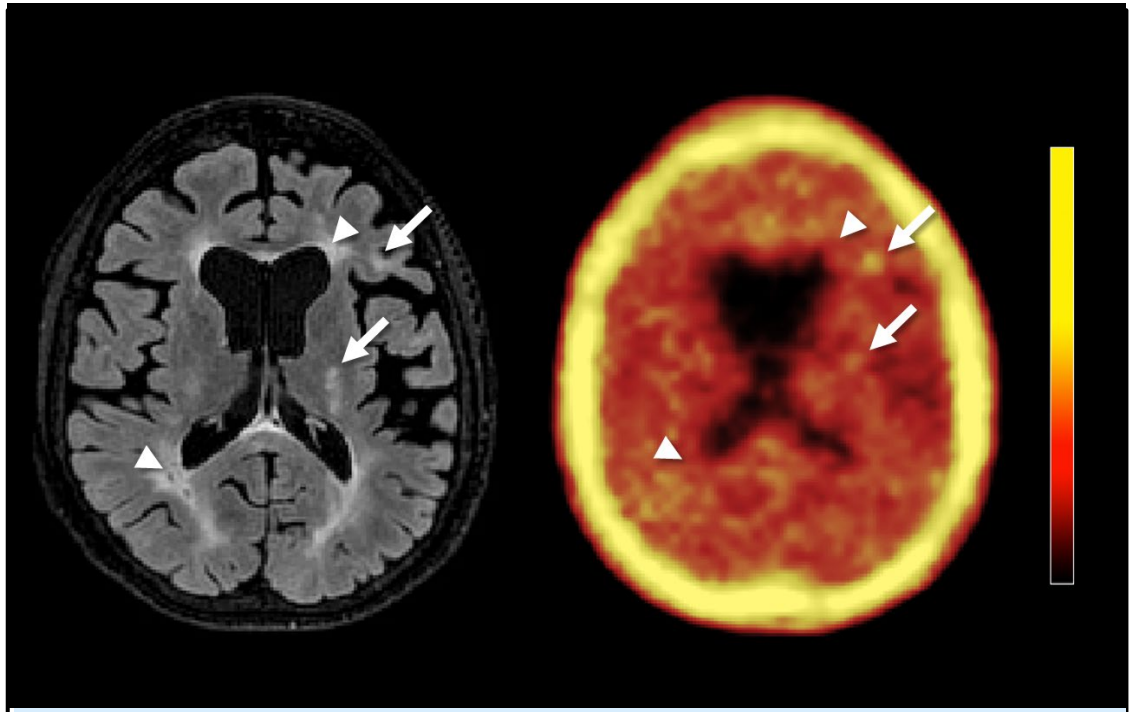


Figure. Baseline MRI T2-FLAIR image (left) and TSPO PBR06 PET SUV map (right) for a representative subject (50-year-old female with active SPMS). The PET tracer map reveals heterogeneity in lesion microglial concentration in lesions that appear otherwise similar on T2-FLAIR MRI. Some lesions (arrows) show substantial TSPO activity, while others (arrowheads) do not.

FLAIR, flair attenuated inversion recovery; MRI, magnetic resonance imaging; PBR, Peripheral benzodiazepine receptor; PET, positron emission tomography; SPMS, secondary progressive multiple sclerosis; SUV, standardized uptake values; TSPO, translocator protein;

Conclusions

- This is the first study evaluating the effect of siponimod on microglia/astrocyte activation as compared with ocrelizumab in patients with aSPMS

- This is also one of the largest and longest, prospective PET MRI study, which will potentially allow to bridge the clinical outcomes (physical and cognitive disability) with a composite of classical and innovative imaging markers (TSPO; USPIO) and fluid biomarkers (NfL + GFAP + Somascan), thereby contributing to advancement in the understanding of prognostic biosignatures for progression in MS

- This study will give key insights into how DMTs (with different mechanisms of action and different brain penetration) affect microglial activation

aSPMS, active secondary progressive multiple sclerosis; DMTs, disease modifying therapies; GFAP, glial fibrillary acidic protein; MRI, magnetic resonance imaging; MS, multiple sclerosis; PET, positron emission tomography; TSPO, translocator protein; USPIO, ultrasmall superparamagnetic iron oxide particles