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Effect of Siponimod on Retinal Thickness, a Potential Marker of Neurodegeneration, in Patients with SPMS: Findings from the EXPAND OCT Substudy

Patrick Vermersch[1], Ralf Gold[2], Amit Bar-Or[3], Bruce A.C. Cree[4], Robert J. Fox[5], Gavin Giovannoni[6], Bingbing Li[7], Jeff Maca[7], Daniela Piani-Meier[8], Goeril Karlsson[8], Ludwig Kappos[9]

[1]Univ. Lille, INSERM U1172, CHU Lille, FHU Precise, Lille, France; [2]Department of Neurology, St Josef-Hospital/Ruhr-University Bochum, Bochum, Germany; [3]Center for Neuroinflammation and Experimental Therapeutics and Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [4]Department of Neurology, UCSF Weill Institute for Neurosciences, University of California San Francisco, San Francisco, CA, USA; [5]Mellen Center for Treatment and Research in Multiple Sclerosis, Neurological Institute, Cleveland, OH, USA; [6]Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom; [7]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [8]Novartis Pharma AG, Basel, Switzerland; [9]Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB), Departments of Head, Spine and Neuromedicine, Clinical Research, Biomedicine and Biomedical Engineering, University Hospital and University of Basel, Basel, Switzerland.

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Introduction

- In people with multiple sclerosis (MS), the inner retinal layers, including the retinal nerve fiber layer (RNFL) and combined ganglion cell and inner plexiform layers (GCIPL), show abnormal thinning over time reflecting neuroaxonal loss[1–3]
- The thinning of retinal layers has been associated with MS-related disability and brain atrophy[4–8], and is more pronounced in progressive MS than in relapsing MS[4]
- The GCIPL has demonstrated reliability, reproducibility and structure-function relationships with visual function and disability in MS[9]
- Optical coherence tomography (OCT) is a noninvasive and convenient tool to quantify the rate of thinning of retinal layers, and therefore could be a potential marker of neurodegeneration, disease progression, and treatment effect of MS therapies[3]

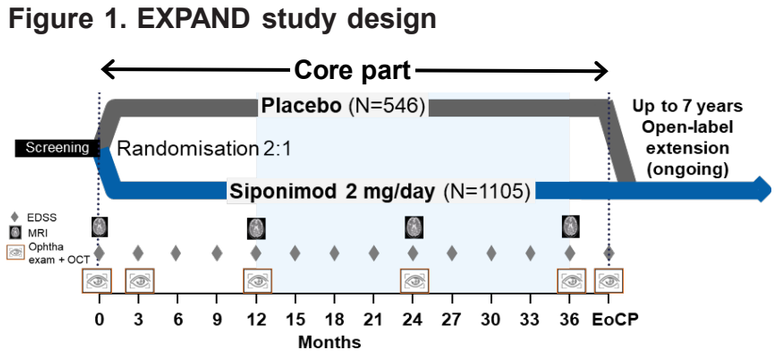
Objectives

- To evaluate the impact of siponimod versus placebo on retinal thinning, as assessed by different OCT measures, in patients with secondary progressive MS (SPMS) who participated in the core part of EXPAND OCT substudy

Methods

- In EXPAND, OCT assessments were done at screening, Month (M) 3, 12, 24 and 36 (**Figure 1**)

Figure 1. EXPAND study design



EDSS, Expanded Disability Status Scale; EoCP, end of Core part; OCT, optical coherence tomography.

Ocular assessments

- The average as well as subfield thickness were measured for
  - Global RNFL and papillo-macular bundle RNFL (pmbRNFL)
  - GCIPL
  - Retinal thickness

Statistical assessments

- Analysis was performed in OCT substudy population, which includes subjects with a baseline and at least one post-baseline OCT measurement in at least one eye rated as a valid assessment
- Longitudinal changes in OCT variables (summary statistics)
- Treatment effects (mixed model repeated measures adjusted for treatment, age, sex and respective baseline OCT variables)
  - Post-hoc sensitivity analysis, adjusted for baseline MRI variables to address imbalances
- Correlation analysis (Pearson product-moment correlation coefficient 'r' for change from baseline) with clinical and MRI endpoints

Results

- The OCT substudy comprised ~10% of the total study population: placebo, N=55; siponimod, N=104 (**Figure 2**)
- At baseline patients in the siponimod group tended to have higher magnetic resonance imaging (MRI) disease activity and lesion volume than the placebo group (**Table 1**)

Figure 2. Patient disposition

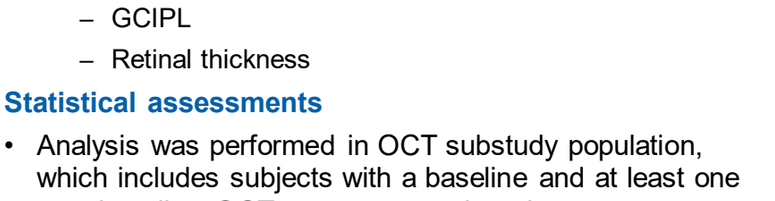


Table 1. Baseline demographic and MS disease characteristics

Mean (SD)	OCT substudy population: Placebo N=55	OCT substudy population: Siponimod N=104	Remaining study population: Total N=1486
Age, years	48.1 (7.4)	48.4 (6.9)	48.0 (7.9)
Female, n (%)	35 (63.6)	58 (55.8)	894 (60.2)
EDSS	5.4 (1.1)	5.3 (1.2)	5.4 (1.1)
SDMT	42.2 (12.3)	39.9 (14.4)	38.9 (13.9)
≥1 Gd+T1 lesion, n (%)	7 (12.7)	19 (18.3)	324 (21.8)
Volume of T1 lesion, mm^3	3923.7 (4278.2)	7006.7 (9205.2)	6556.6 (8505.4)
Volume of T2 lesions, mm^3	10717.5 (10666.7)	15658.2 (16825.9)	15431.6 (16091.1)
Normalised brain volume, cc	1431.4 (81.5)	1414.8 (85.0)	1423.0 (87.1)

EDSS, Expanded Disability Status Scale; Gd+, gadolinium–enhancing; OCT, optical coherence tomography; SD, standard deviation; SDMT, Symbol Digit Modalities Test.

- At baseline, mean thickness of OCT measures were slightly lower in the siponimod group compared to the placebo group (**Table 2**)

Table 2. Baseline OCT characteristics

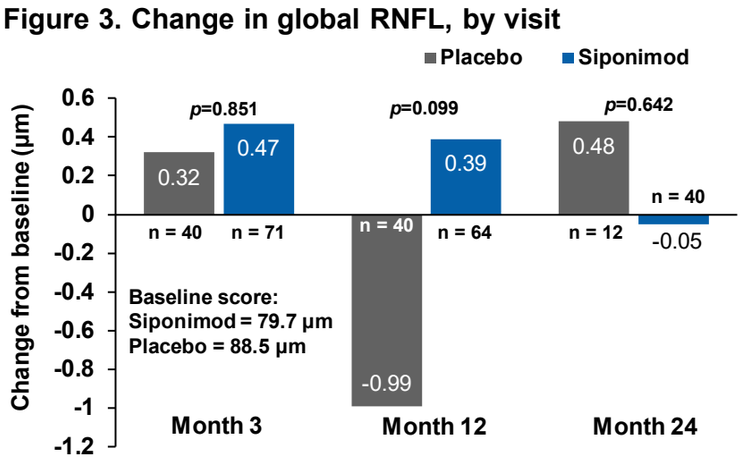
Mean	OCT substudy population: Placebo N=55	OCT substudy population: Siponimod N=104
LCVA, decimal‡	n=54/53 0.95/0.93	n=103/103 0.89/0.85
Global RNFL, µm	n=26/25 87.6/89.5	n=43/41 80.7/78.6
GCIPL, µm	n=55/54 70.3/70.1	n=101/100 66.6/65.8
Retinal thickness, µm	n=55/54 303.97/302.83	n=102/101 300.15/300.31

GCIPL, ganglion cell and inner plexiform layer; LCVA, lower contrast visual acuity; N, number of patients; n, number of eyes; OCT, optical coherence tomography; RNFL, retinal nerve fiber layer.
‡Untransformed.

RNFL

- Global RNFL thickness at M12 numerically favored siponimod but not at M24 (low number of assessments noted; **Figure 3**). Consistent results were observed after adjusting for baseline MRI variables (M12: p=0.055; M24: p=0.88)
- Subfield areas had numerically lesser thinning in siponimod versus placebo; this was most prominent in temporal superior RNFL thickness (change at M24: −0.41 µm vs −5.62 µm)
- No significant effects on pmbRNFL thickness

Figure 3. Change in global RNFL, by visit



n, number of eyes with valid OCT assessment.

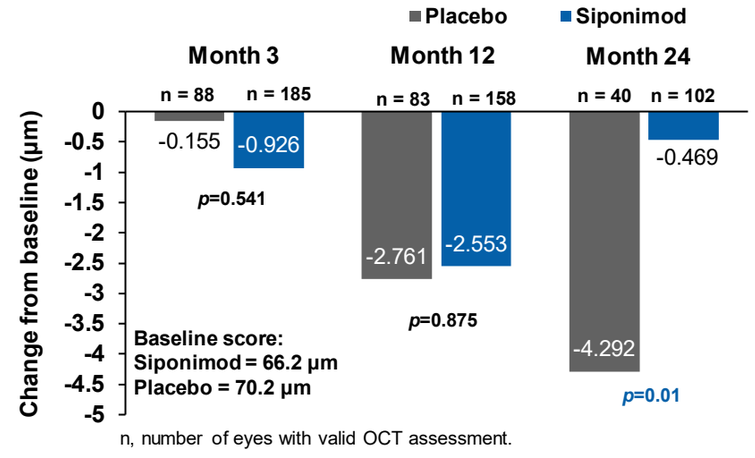
GCIPL

- Less thinning in GCIPL over time with siponimod versus placebo was observed at M12 and M24 (**Figure 4**) sensitivity analysis findings were consistent (M24: −0.56 vs −4.48; p=0.01)
- For all subfield areas, the decrease in thickness was consistently greater in the placebo group compared to siponimod group (data not shown)

Retinal thickness

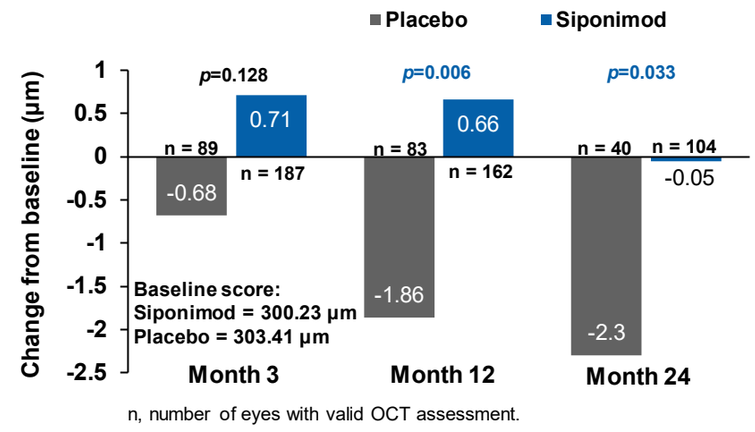
- A consistent decrease in retinal thickness was observed over time for placebo; the difference was statistically significant in favor of siponimod at both M12 and M24 (**Figure 5**). Sensitivity analysis findings were consistent (M12: p=0.015; M24: p=0.036)

Figure 4. Change in GCIPL thickness, by visit



n, number of eyes with valid OCT assessment.

Figure 5. Change in retinal thickness, by visit



n, number of eyes with valid OCT assessment.

- All subfield areas showed greater thinning in the placebo group than in siponimod group, with the central area showing increase with siponimod (data not shown)

Correlation analysis

- Low positive correlations (r, ranging between 0.22 to 0.47) were only found for some parameters at M24, possibly due to low sample size (data not shown)

Conclusions:

- Small number of participants and variability in the OCT measures are limitations of this substudy
- Despite these limitations, siponimod showed significant treatment effect in reducing GCIPL thinning (Month 24), and global retinal thinning (Months 12 and 24)
- The effect on RNFL and pmbRNFL was variable, possibly due to small number of assessments, although sensitivity analysis suggests trends favouring siponimod
- Across OCT measures, in all subfield areas, thinning was lessened with siponimod as compared to placebo
- These OCT findings appear to be in line with previously reported beneficial effects of siponimod on other outcomes related to neurodegeneration, including grey matter atrophy and magnetisation transfer ratio (MTR) changes in normal appearing brain tissues
  - Several preclinical studies suggest siponimod impacts neurodegenerative processes and may promote remyelination (Posters at ECTRIMS 2021*)
- Further investigation in a larger patient population is needed to confirm these findings

*1. Basavarajappa D, et al. **eP32-P718**; 2. Windener F, et al. **Scientific Session 17–173**; 3. Dietrich M, et al. **Scientific Session 17–174.**

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Disclosures

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