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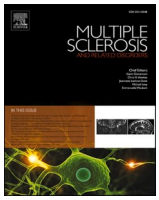

Effect of siponimod on retinal thickness, a marker of neurodegeneration, in participants with SPMS: Findings from the EXPAND OCT substudy

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ABSTRACT

Background: People with MS show abnormal thinning of the retinal layers, which is associated with clinical disability and brain atrophy, and is a potential surrogate marker of neurodegeneration and treatment effects.
Objective: To evaluate the utility of retinal thickness as a surrogate marker of neurodegeneration and treatment effect in participants with secondary progressive MS (SPMS) from the optical coherence tomography (OCT) substudy of the EXPAND Phase 3 clinical trial (siponimod versus placebo).
Methods: In the OCT substudy population ($n = 159$), treatment effects on change in the average thickness of the retinal layer, peripapillary retinal nerve fiber layer (pRNFL), and combined macular ganglion cell and inner plexiform layers (GCIPL) were analyzed by high-definition spectral domain OCT at months 3, 12, and 24.
Results: Thinning from baseline was observed across all retinal layers and time points in the placebo group. Siponimod significantly reduced GCIPL thinning versus placebo at month 24 (adjusted mean [SE] [μm]: −0.47 [0.81] vs. −4.29 [1.23]; $p = 0.01$), and overall retinal thinning at months 12 (+0.66 [0.54] vs. −1.86 [0.75]; $p = 0.006$) and 24 (−0.05 [0.59] vs. −2.30 [0.88]; $p = 0.033$). Although not significant, results for pRNFL consistently followed the same trends.
Conclusion: This exploratory substudy supports further investigation of OCT measurement of retinal atrophy as a non-invasive potential biomarker of treatment effects on neurodegeneration in SPMS.

1. Introduction

In people with multiple sclerosis (MS), the retinal layers show abnormal thinning over time reflecting neuroaxonal loss (Green et al., 2010; Khanifar et al., 2010; Kuchling and Paul, 2020; Parisi et al., 1999; Paul et al., 2021; Petzold et al., 2017). Measurements of retinal layer thinning by optical coherence tomography (OCT) are highly reproducible, allowing longitudinal follow-up of retinal structures (Garcia-Martin

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et al., 2011; Paul et al., 2021). Not confounded by myelin, OCT measures have a spatial resolution (~5 μm) approximately 2–3 orders of magnitude greater than magnetic resonance imaging (MRI), making OCT an ideal tool for assessing neuroaxonal degeneration and treatment effects (Alonso et al., 2018; García-Martín et al., 2010; Graves, 2019; Mehmood et al., 2021; Paul et al., 2021; Siger et al., 2008).

Thinning of retinal layers is associated with MS-related disability, brain atrophy, and disability progression (Alonso et al., 2018; Frau et al., 2018; Gordon-Lipkin et al., 2007; Martinez-Lapiscina et al., 2016; Mirmosayyeb et al., 2023; Oertel et al., 2019; Paul et al., 2021; Saidha et al., 2015; Swinnen et al., 2023; Vidal-Jordana et al., 2020). Retinal layers include the peripapillary retinal nerve fiber layer (pRNFL), which contains primarily unmyelinated axons emerging from retinal ganglion cell neurons, and the combined ganglion cell and inner plexiform layers (GCIPL), where the axons forming pRNFL originate (Petzold et al., 2017). While some evidence suggests that retinal (more specifically GCIPL) and whole brain atrophy are more strongly associated in progressive MS than in relapsing MS (Saidha et al., 2015), other studies questioned this association in the later stage of the disease due to a plateau or 'floor effect' wherein pRNFL and GCIPL atrophy can no longer be detected below a certain level of total thickness (Balk et al., 2016; Winges et al., 2019).

EXPAND was the largest Phase 3 study of participants with secondary progressive MS (SPMS) to date ($N = 1651$) and siponimod was the first disease-modifying therapy approved in this population (Cree et al., 2022; Kappos et al., 2018). The EXPAND OCT substudy was conducted in a subgroup of EXPAND participants. The objective was to explore the utility of the OCT-measured average retinal layer thickness (including average pRNFL and papillo-macular bundle RNFL [pmbRNFL], GCIPL, and overall retinal thickness) and their subfields as potential markers of axonal degeneration and disability progression in SPMS. The treatment effect on thinning of the different retinal layers, as well as correlations of OCT measures with clinical and radiological outcomes, was explored.

2. Methods

2.1. Study design and participants

The core part of the EXPAND trial (NCT01665144) was an event-driven, randomized, multicenter, double-blind, placebo-controlled, parallel-group study of variable duration (median 21 months [range 0.2–37.0]) in 1651 participants with SPMS from 294 sites randomized (2:1) to receive either siponimod or placebo (Fig. 1). Details of the EXPAND study including inclusion and exclusion criteria were presented in Kappos et al. (Kappos et al., 2018). This OCT substudy included 159 participants at a subset of sites (29), whose participation was based on access to high-definition (HD) spectral domain OCT machines. Because this substudy was purely exploratory, no pre-defined number of participants was required, and no additional inclusion/exclusion criteria had to be fulfilled. A sensitivity analysis was performed in a subgroup of participants within the substudy, in which those with ongoing ophthalmic disease at the time of screening were excluded (restricted analysis set).

2.2. Optical coherence tomography (OCT)

OCT assessments were performed for all participants from the substudy at screening; months 3, 12, 24, 36; and end of treatment/end of study using HD spectral domain OCT machines (including Spectralis™ HRA+OCT [Heidelberg Engineering, Germany] and Cirrus HD-OCT™ [Zeiss, Germany]). The number of available observations at month 36 was very low (three participants) and precluded any conclusions to be drawn. The standard procedure for the acquisition and transmission of OCT examination data was provided in an OCT manual to the sites. Either Nsite-software or standard ophthalmology software were used for image acquisition. OCT images were transferred (blinded to participant name and date of birth) to an independent OCT reading center (Bern Photographic Reading Center [BPRC]) for central evaluation. A

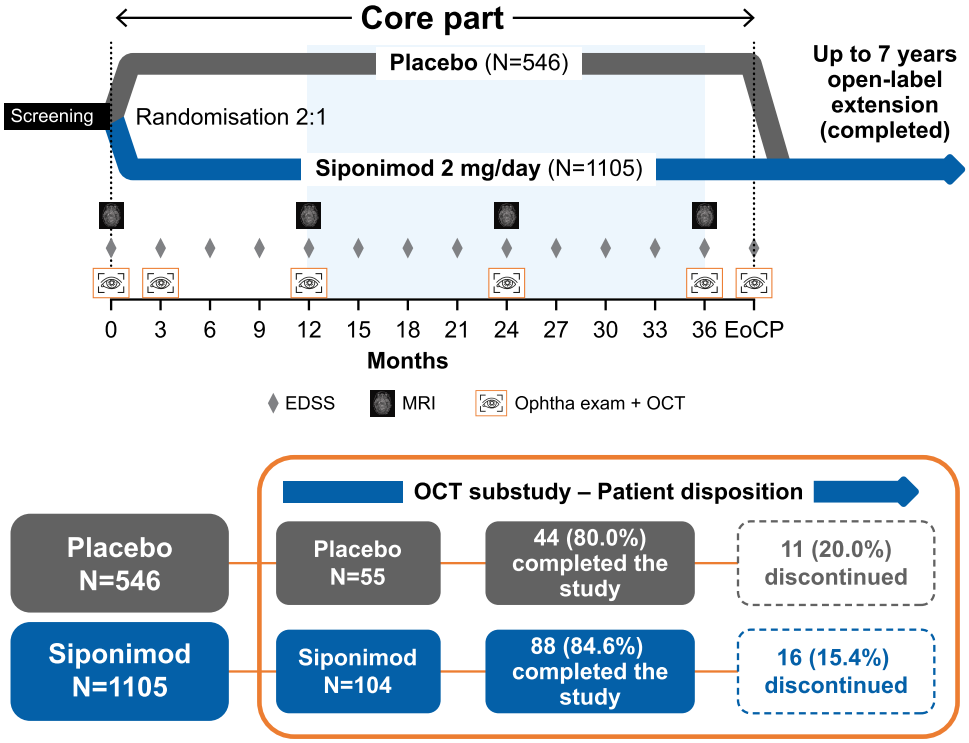

Fig. 1. EXPAND and OCT substudy design. In the core part OCT assessments were performed at screening and months 3, 12, 24 and 36. Open-label started when patient had an "event." EDSS, Expanded Disability Status Scale; EoCP, end of core phase; OCT, optical coherence tomography; ophtha exam, ophthamologic examination.

qualified reader at BPRC performed the image grading applying standardized measurement algorithms for retinal thickness and sublayer segmentation. The assessments were conducted and described in accordance to the quality control criteria at the BPRC, which contributed to the establishment of the OSCAR-IB and APOSTEL criteria (Cruz-Herranz et al., 2016; Schippling et al., 2015), now standard for reporting OCT study results. No minimum quality level was defined. The detailed OCT scanning protocol is provided as supplementary data. pRNFL thickness was measured either from the optic nerve head scans (on a circular ring around the optic nerve head; Spectralis) or derived from the optic disc cube scan (Cirrus). Besides the main pRNFL thickness on the ring ('average pRNFL thickness'), various segments of the ring were also measured separately. Subfield areas of mean pRNFL thickness were temporal, nasal superior, temporal superior, nasal inferior, and temporal inferior. The papillo-macular bundle (pmb) thickness was also measured and analyzed (measure available for sites using Spectralis only). GCIPL thickness and overall retinal thickness as well as their respective subfields (central area, inner superior, inner temporal, inner inferior, and inner nasal) were derived from macular cube scans (Spectralis or Cirrus). The thickness of each OCT parameter and subfield was calculated as the mean value of all Amplitude scans (A-scans; type of scan that measure distances between layers with different light reflectances) in the related area.

2.3. Statistical methodology

Participants of the OCT substudy had a baseline and one or more postbaseline OCT measurements in at least one eye rated as a valid assessment (Fig. 1). The end of treatment/end of study assessments if available were mapped to protocol scheduled visits according to prespecified visit-windows/time points. Summary statistics were provided for the change from baseline in the OCT variables (average pRNFL thickness, pmb thickness, GCIPL thickness, overall retinal thickness, and their subfields) by eye (left, right and both), time point and treatment. The between treatment difference in change from baseline in the OCT variables of interest were assessed using a mixed-model repeated measures (MMRM) approach to consider results from all available time points. The model was adjusted for treatment, age, sex, time point, treatment by time point interaction, and respective baseline OCT variables. The result from each time point were nested in eye and participant to allow for inter-eye and intra-participant dependencies. No adjustment for multiplicity was performed; p-value < 0.05 will be interpreted as 'nominally' significant rather than statistically significant.

A post hoc sensitivity analysis was conducted with adjustment for baseline MRI variables and MS duration as additional covariates to address imbalances in disease characteristics between treatment groups. Another post hoc sensitivity analysis assessed the treatment effect on the percentage change from baseline for each of the OCT measures.

Correlations (based on Pearson's coefficient [r]) were explored graphically between the main OCT variables of interest and the following clinical and visual acuity variables: percentage brain volume change from baseline (overall, cortical grey matter, thalamus) and change from baseline in: Expanded Disability Status Scale (EDSS) score; Symbol Digit Modalities Test (SDMT) score; lower contrast visual acuity (LCVA) score; T2 lesion volume (transformed by taking the cube root since this has shown to produce linear relationships when compared to pRNFL thickness); and T1 hypointense lesion volume.

2.4. Ethics

The study protocol and all amendments were reviewed by the Independent Ethics Committee or Institutional Review Board for each center. The study was conducted according to the International Council for Harmonization E6 Guideline for Good Clinical Practice that have their origin in the Declaration of Helsinki (World Medical Association, 2024).

Table 1
Baseline demographics and disease characteristics.

	OCT substudy population[a]		Remaining study population[b]
	Placebo, $N = 55$	Siponimod, $N = 104$	Total, $N = 1486$
Age, years	48.1 (7.4)	48.4 (6.9)	48.0 (8.0)
Female, n (%)	35 (63.6)	58 (55.8)	894 (60.2)
Race, n (%)			
White	51 (92.7)	102 (98.1)	1406 (94.6)
Black or African American	3 (5.5)	2 (1.9)	5 (0.3)
Asian	0 (0.0)	0 (0.0)	48 (3.2)
Unknown	0 (0.0)	0 (0.0)	10 (0.7)
Other	1 (1.8)	0 (0.0)	17 (1.1)
Ethnicity, n (%)			
Hispanic or Latino	12 (21.8)	17 (16.3)	77 (5.2)
Not Hispanic or Latino	30 (54.5)	52 (50.0)	1151 (77.5)
Not reported	6 (10.9)	11 (10.6)	136 (9.2)
Unknown	7 (12.7)	24 (23.1)	122 (8.2)
EDSS	5.4 (1.1)	5.3 (1.2)	5.4 (1.1)
SDMT	42.2 (12.3)	39.9 (12.7)	38.9 (13.9)
≥1 Gd+ T1 lesion at baseline, n (%)	7 (12.7)	19 (18.3)	324 (21.8)
Patients with no relapses in the last year prior to screening, n (%)	44 (80.0)	81 (77.9)	1165 (78.4)
Number of relapses in the last year prior to screening	0.3 (0.6)	0.3 (0.6)	0.3 (0.6)
Number of relapses in the last 2 years prior to screening	0.6 (1.4)	0.6 (1.1)	0.7 (1.2)
Volume of T1 lesions, mm^3	3923.7, (4278.2)	7006.7, (9205.2)	6556.6, (8505.4)
Volume of T2 lesions, mm^3	10,717.5, (10,666.7)	15,658.2, (16,825.9)	15,431.6, (16,091.1)
Normalized brain volume, cc	1431.4 (81.5)	1414.8 (85.0)	1423.0 (87.1)
MS duration since diagnosis, years	10.8 (7.2)	13.3 (8.2)	12.6 (7.7)
MS duration since first symptom, years	14.1 (7.9)	17.7 (8.7)	16.8 (8.3)
Time since conversion to SPMS, years	2.7 (1.9)	3.6 (3.9)	3.8 (3.5)

Data are expressed as mean (SD) unless specified otherwise.

[a] OCT substudy FAS, a subset of FAS that includes participants with a baseline and at least one postbaseline OCT measurement in at least one eye rated as a valid assessment.

[b] Includes FAS participants that are not in the OCT FAS. N is the number of participants in the corresponding group. EDSS, Expanded Disability Status Scale; FAS, full analysis set; Gd+, gadolinium-enhancing; MRI, magnetic resonance imaging; OCT, optical coherence tomography; SD, standard deviation; SDMT, Symbol Digit Modalities Test.

All participants gave written informed consent before screening. The study information included the evaluation of OCT images obtained during the study as part of ophthalmic examinations.

3. Results

3.1. Participants

The OCT full analysis set comprised 159 participants (approximately 10 % of the EXPAND population); 104 participants in the siponimod group and 55 participants in the placebo group. Baseline demographic characteristics were generally balanced across the two groups. The mean age was 48.3 years. The majority of participants were female (58.5 %) and White (96.2 %). The proportions in each category were similar to those observed in the remaining EXPAND core part except for the higher proportion of participants of Hispanic and Latino origin in the substudy (Table 1).

Groups generally had similar baseline characteristics in line with the overall study population, except for some imbalance observed for disease duration/time since conversion to SPMS, T2 lesion volume and level of inflammatory activity at baseline, suggesting that MS disease in the placebo group was somewhat less severe/advanced than in the siponimod group and the rest of the study population. (Table 1). A total of 7 participants (6.7 %) in the siponimod group had a history of optic neuritis, compared to 3 participants (5.5 %) in the placebo group. Among these, 4 participants (3.8 %) in the siponimod group and 1 participant (1.8 %) in the placebo group had ongoing optic neuritis at the time of screening. The mean thickness of OCT parameters at baseline was also consistently slightly lower in the siponimod group compared with the placebo group (Table 2). Most (97.5 %) participants were scanned using the same device throughout the study; only four patients had their final visit performed on a different platform.

3.2. Longitudinal analysis of OCT parameters

The change of average pRNFL thickness, GCIPL thickness and overall retinal thickness is presented in Fig. 2.

Table 2
Baseline ocular related characteristics at eye level.

Mean	OCT substudy population[a]			
	Placebo, $N = 55$		Siponimod, $N = 104$	
	Right eye	Left eye	Right eye	Left eye
LCVA, logMAR	$n = 54$ 0.04 (0.12)	$n = 53$ 0.06 (0.22)	$n = 103$ 0.07 (0.17)	$n = 103$ 0.12 (0.25)
Global RNFL, µm	$n = 53$ 85.0 (13.6)	$n = 52$ 84.0 (13.7)	$n = 98$ 79.1 (13.5)	$n = 96$ 77.7 (14.9)
GCIPL, µm	$n = 55$ 70.3 (12.7)	$n = 54$ 70.1 (12.4)	$n = 101$ 66.6 (11.8)	$n = 100$ 65.7 (12.1)
Retinal thickness, µm	$n = 55$ 304.0 (21.9)	$n = 54$ 302.8 (21.7)	$n = 102$ 300.2 (21.6)	$n = 101$ 300.3 (20.6)

Data are expressed as mean (SD) unless specified otherwise.

[a] OCT substudy FAS, a subset of FAS that includes participants with a baseline and at least one postbaseline OCT measurement in at least one eye rated as a valid assessment. GCIPL thickness derived as the average of central area, inner inferior, inner nasal, inner superior and inner temporal GCIPL thickness if at least 4 out of 5 measurements are nonmissing at the respective visit, by right and left eye respectively. Retinal thickness derived as the average of central area inner inferior, inner nasal, inner superior and inner temporal thickness if at least 4 out of 5 measurements are nonmissing at the respective visit, by right and left eye respectively. N is the number of participants in the FAS; n is the number of participants with nonmissing value. FAS, full analysis set; GCIPL, ganglion cell and inner plexiform layers; LCVA, lower contrast visual acuity; OCT, optical coherence tomography; RNFL, retinal nerve fiber layer.

3.2.1. Average pRNFL and pmbRNFL thickness

In the model-based analysis, a consistent numerical decrease in average pRNFL thickness from baseline was observed in the placebo group at months 3, 12 and 24; this was not the case for the siponimod group, wherein the average pRNFL thickness remained stable through month 24. The differences between treatment groups were not significant (Fig. 2A). No clear trend in change in mean pmbRNFL thickness over time was observed with either siponimod or placebo and there was no significant difference in the change from baseline in pmbRNFL thickness at any time point between the treatment groups (data not shown).

3.2.2. GCIPL thickness

For GCIPL thickness, a decrease over time was observed for placebo at months 12 and 24 (Fig. 2B). A similar decrease was seen in the siponimod group at month 12, but not at month 24, where a nominally significant difference in favor of siponimod was found (adjusted mean [SE]: −0.47 [0.81] µm with siponimod vs −4.29 [1.23] µm with placebo, $p = 0.01$).

3.2.3. Overall retinal thickness

A consistent decrease in mean retinal thickness was observed over time for placebo, but not for siponimod (Fig. 2C). This difference favored siponimod from month 12 onwards, with adjusted mean (SE) of siponimod versus placebo of +0.66(0.54) µm versus −1.86(0.75) µm ($p = 0.006$) at month 12 and −0.05(0.59) µm versus −2.30(0.88) µm ($p = 0.033$) at month 24.

3.3. Sensitivity analyses

The results of sensitivity analyses after adjusting for baseline MRI variables and duration of MS since first symptom were consistent with the preplanned analyses across all OCT measures. Percentage changes from baseline were in line with absolute changes across all OCT measures (Supplementary Fig. 1). The sensitivity analyses performed on the restricted OCT analysis set excluding participants with ongoing ophthalmic disease produced similar results for all OCT thickness measures and time points.

3.4. Subfields areas

At month 24, across all OCT measures, all the subfield areas except for the temporal pRNFL consistently showed numerically less thinning in participants treated with siponimod compared to those treated with placebo (Fig. 3). The treatment effect on thinning was nominally significant for most GCIPL subfields (central, inner superior, inner temporal, inner nasal) (Fig. 3B); however, no significance was reached for most pRNFL and retinal subfields (Fig. 3A and C).

3.5. Correlation between OCT variables and MRI and clinical outcomes

For the overall sub-study population, no correlation was apparent between change from baseline in any of the main OCT variables (average pRNFL, pmbRNFL, GCIPL, and overall retinal thickness) and percentage brain volume change, or changes in EDSS, SDMT, LCVA, T2 lesion volume, and T1 hypointense lesion volume from baseline. Low correlations were found at month 24 between change from baseline in pmbRNFL (r = 0.31 and 0.39 for the right and left eye, respectively) or overall retinal thickness (r 0.47 and 0.22 for the right and left eye, respectively) and change from baseline in cortical grey matter volume. A low correlation was found between the change from baseline in GCIPL thickness and the change from baseline in EDSS at month 24 ($r = 0.37$ and 0.31 for the right and left eye, respectively). This positive correlation, suggesting that a worsening of EDSS was associated with higher GCIPL thickness, was weak and mostly driven by two data points only.

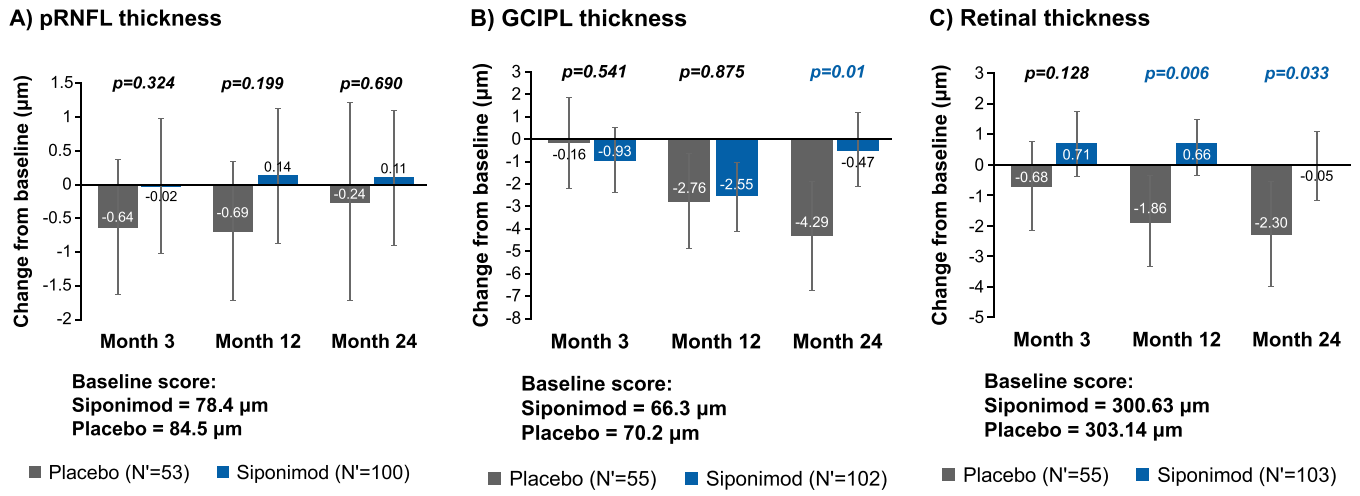

Fig. 2. Adjusted means (95 % CI) of change from baseline in retinal layers. A) pRNFL thickness; B) GCIPL thickness; C) retinal thickness. GCIPL thickness was calculated as the average of central area, inner inferior, inner nasal, inner superior and inner temporal GCIPL thickness if at least 4 out of 5 measurements were nonmissing at the respective visit, for the right and left eye, respectively. Retinal thickness was calculated as the average of the central area, inner inferior, inner nasal, inner superior and inner temporal thickness if at least 4 out of 5 measurements were nonmissing at the respective visit, for the right and left eye, respectively. Negative values correspond to a decrease from baseline. CI, confidence interval; GCIPL, ganglion cell and inner plexiform layers; pRNFL, peripapillary retinal nerve fiber layer. N' is the number of participants included in the analysis (i.e., with at least one postbaseline value and nonmissing covariates). Models were adjusted for treatment, age, sex, baseline value and treatment by time point interaction.

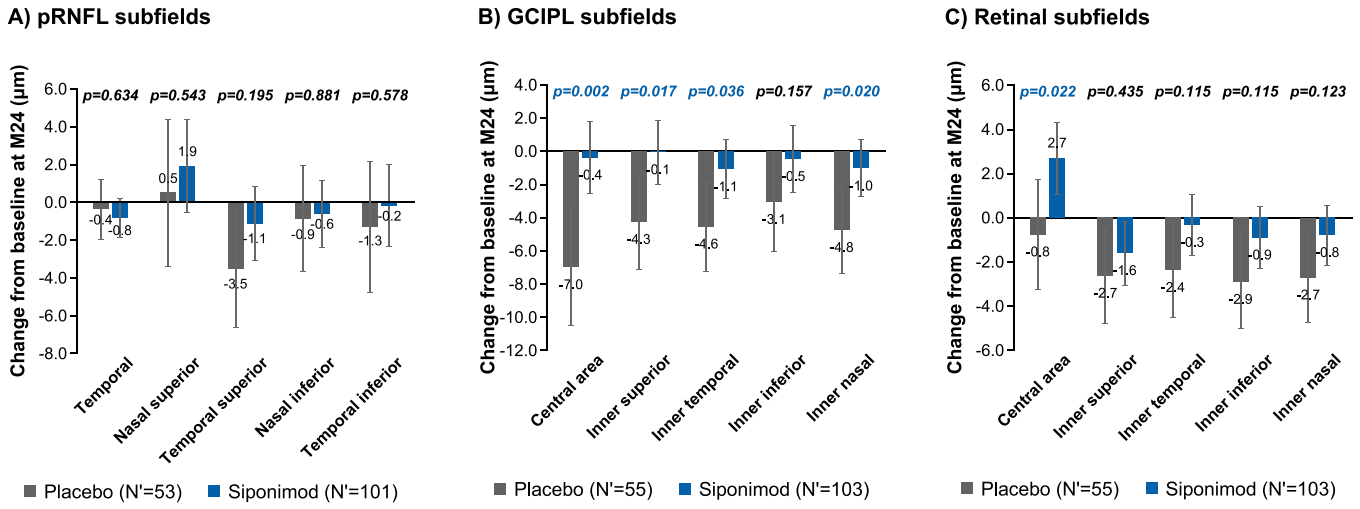

Fig. 3. Adjusted means (95 % CI) of change from baseline in retinal subfields. A) pRNFL subfields; B) GCIPL subfields; C) retinal subfields. Negative values correspond to a decrease from baseline. CI, confidence interval; GCIPL, ganglion cell and inner plexiform layers; pRNFL, peripapillary retinal nerve fiber layer. N' is the number of participants included in the analysis (i.e., with at least one postbaseline value and nonmissing covariates). The models were adjusted for treatment, age, sex, baseline value and treatment by time point interaction.

4. Discussion

This OCT substudy, conducted as part of the core part of the EXPAND study, was designed to evaluate change in the OCT-measured thickness of several retinal layers in participants with SPMS treated with siponimod versus placebo and followed for 2 years (variable duration up to 3 years). The objective was to explore the utility of retinal layer thickness (e.g. average pRNFL, pmbRNFL, GCIPL, and overall retinal thickness) as markers of treatment effects on neuroaxonal degeneration and disability progression in SPMS. Treatment with siponimod significantly reduced GCIPL thinning at month 24, and overall retinal thinning at months 12 and 24. Although the treatment effects for the other time points and other thickness parameters, including pRNFL and pmbRNFL, were not statistically significant, most of the numerical differences consistently favored siponimod versus placebo. The change in subfield thickness also consistently showed similar trends, reaching nominal significance ($p \leq$ 0.05) for most GCIPL subfields.

Such consistency in treatment-related changes despite the small sample size supports the rationale of using OCT and retinal thickness measurements as an endpoint in clinical trials of progressive MS disease. This is in line with the approach taken by several such trials including SPRINT-MS, FLUOX-PMS, ACTiMuS, or SMART-MS (Lambe et al., 2020; Oertel et al., 2019). While many of these studies are ongoing, or with results not yet published, a post-hoc analysis of phase 2 SPRINT-MS showed that treatment with ibudilast decreased GCIPL atrophy versus placebo in progressive MS (Ehrhardt et al., 2023). The authors, however, noted that this treatment effect was driven by participants with primary progressive MS (PPMS), rather than those with SPMS. According to the researchers, this observation possibly was consistent with the faster brain atrophy in the PPMS cohort, making treatment effects more likely to be detected in this subtype.

Our finding demonstrating a treatment effect of siponimod on GCIPL

is also in line with previous evidence suggesting that change in thickness of GCIPL is a more clinically meaningful biomarker of CNS atrophy than RNFL (thickness). GCIPL is more strongly correlated with visual dysfunction (Saidha et al., 2011) and its decrease is more severe and can be detected much earlier (Gabilondo et al., 2015; Pietroboni et al., 2020) compared with the RNFL layer. These results support the hypothesis that neurodegeneration in this SPMS population may arise from neuronal cell damage (as measured by GCIPL change), more so than only axonal degeneration (as measured by RNFL), consistent with previous observations in RRMS (Paul et al., 2021; Pietroboni et al., 2020).

The RNFL and macular ganglion cells are affected by MS in parallel to clinical and paraclinical parameters, including physical disability, cognitive disorders as well as cerebral atrophy in MRI (Alonso et al., 2018; Mehmood et al., 2021). In our analysis, low correlations were observed between some OCT measures (pmbRNFL and retinal thinning) and change in cortical grey matter volume after 1 year; however, no meaningful correlation was observed between OCT parameters and the other measured clinical or MRI outcomes (EDSS, SDMT, LCVA, T2 lesion volume, and T1 hypointense lesion volume).

This negative result likely reflects one main limitation of this study, inherent to its exploratory nature, which is the small sample size and insufficient statistical power to consistently detect a treatment effect on OCT parameters and their correlations with disease outcomes. Based on our results on GCIPL changes, the estimated sample size with a power of over 90 % to detect a difference of 3 μm between two treatment groups assuming 1:1 randomization would be at least 300 (i.e. 150 participants in each group). Our effect size (approximatively 40 %) and related sample size calculation is in line with that derived from the SPRINT-MS trial of ibudilast in progressive MS (Ehrhardt et al., 2023). In addition, although baseline demographics were generally balanced, baseline disease activity was lower, and OCT measures were better in the placebo group, potentially biasing the results (since higher baseline thickness allows a larger dynamic range from which the retinal layer can thin). Sensitivity analyses were conducted to address these limitations; adjusting for baseline imbalance in disease characteristics yielded results in line with the unadjusted results, and treatment effects on percentage changes in retinal layers thickness were consistent with effects on absolute changes. Another limitation may be related to the improving performance and sensitivity of OCT imaging techniques and post-acquisition analyses, which may not have been optimal at the time this analysis was conducted. This could partly explain the high variability in OCT measures observed in our study, including steep decrease or apparent increase in some of the retinal thickness measures. Such variability, however, also likely reflects some degree of physiological variation in line with earlier reports (Balk et al., 2014, 2012).

In conclusion, the consistent trend in treatment-related OCT changes across all retinal layers and subfields observed in the EXPAND OCT substudy, despite its exploratory nature, supports the utility of OCT as a potential non-invasive biomarker to evaluate treatment effects on retinal layer atrophy in participants with SPMS; however, more results from ongoing or future trials in larger SPMS populations are needed to confirm these findings and establish OCT as a marker of neurodegeneration and its correlation with clinical and MRI outcomes in SPMS.

Data sharing

Novartis is committed to sharing with qualified external researchers access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided is anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. This trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com

CRediT authorship contribution statement

Patrick Vermersch: Supervision, Writing – review & editing. **Ralf Gold:** Supervision, Writing – review & editing. **Amit Bar-Or:** Supervision, Writing – review & editing. **Bruce A.C. Cree:** Supervision, Writing – review & editing. **Robert J. Fox:** Supervision, Writing – review & editing. **Gavin Giovannoni:** Supervision, Writing – review & editing. **Friedemann Paul:** Writing – review & editing. **Sebastian Wolf:** Supervision, Writing – review & editing. **Bingbing Li:** Software, Writing – review & editing. **Marie-Catherine Mousseau:** Visualization, Writing – original draft, Writing – review & editing. **Tina Maio-Twofoot:** Writing – review & editing. **Xiaofang Shi:** Project administration, Writing – review & editing. **Ludwig Kappos:** Supervision, Writing – review & editing.

Declaration of competing interest

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Supplementary materials

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References

Alonso, R., Gonzalez-Moron, D., Garcea, O., 2018. Optical coherence tomography as a biomarker of neurodegeneration in multiple sclerosis: a review. Mult Scler Relat Disord 22, 77–82. https://doi.org/10.1016/j.msard.2018.03.007.

Balk, L.J., Cruz-Herranz, A., Albrecht, P., Arnow, S., Gelfand, J.M., Tewarie, P., Killestein, J., Uitdehaag, B.M., Petzold, A., Green, A.J., 2016. Timing of retinal neuronal and axonal loss in MS: a longitudinal OCT study. J Neurol 263 (7), 1323–1331. https://doi.org/10.1007/s00415-016-8127-y.

Balk, L.J., Oberwahrenbrock, T., Uitdehaag, B.M., Petzold, A., 2014. Physiological variation of retinal layer thickness is not caused by hydration: a randomised trial. J Neurol Sci 344 (1–2), 88–93. https://doi.org/10.1016/j.jns.2014.06.031.

Balk, L.J., Sonder, J.M., Strijbis, E.M., Twisk, J.W., Killestein, J., Uitdehaag, B.M., Polman, C.H., Petzold, A., 2012. The physiological variation of the retinal nerve fiber layer thickness and macular volume in humans as assessed by spectral domain-optical coherence tomography. Invest Ophthalmol Vis Sci 53 (3), 1251–1257. https://doi.org/10.1167/iovs.11-8209.

Cree, B.A., Arnold, D.L., Fox, R.J., Gold, R., Vermersch, P., Benedict, R.H., Bar-Or, A., Piani-Meier, D., Rouyrre, N., Ritter, S., Kilaru, A., Karlsson, G., Giovannoni, G., Kappos, L., 2022. Long-term efficacy and safety of siponimod in patients with secondary progressive multiple sclerosis: analysis of EXPAND core and extension data up to >5 years. Mult Scler 28 (10), 1591–1605. https://doi.org/10.1177/13524585221083194.

Cruz-Herranz, A., Balk, L.J., Oberwahrenbrock, T., Saidha, S., Martinez-Lapiscina, E.H., Lagreze, W.A., Schuman, J.S., Villoslada, P., Calabresi, P., Balcer, L., Petzold, A., Green, A.J., Paul, F., Brandt, A.U., Albrecht, P., 2016. The APOSTEL recommendations for reporting quantitative optical coherence tomography studies. Neurology 86 (24), 2303–2309. https://doi.org/10.1212/wnl.0000000000002774.

Ehrhardt, H., Lambe, J., Moussa, H., Vasileiou, E.S., Kalaitzidis, G., Murphy, O.C., Filippatou, A.G., Pellegrini, N., Douglas, M., Davis, S., Nagy, N., Quiroga, A., Hu, C., Zambriczki Lee, A., Duval, A., Fitzgerald, K.C., Prince, J.L., Calabresi, P.A., Sotirchos, E.S., …Saidha, S., 2023. Effects of Ibudilast on Retinal Atrophy in Progressive Multiple Sclerosis Subtypes: post Hoc Analyses of the SPRINT-MS Trial. Neurology 101 (10), e1014–e1024. https://doi.org/10.1212/wnl.0000000000207551.

Frau, J., Fenu, G., Signori, A., Coghe, G., Lorefice, L., Barracciu, M.A., Sechi, V., Cabras, F., Badas, M., Marrosu, M.G., Cocco, E., 2018. A cross-sectional and longitudinal study evaluating brain volumes, RNFL, and cognitive functions in MS patients and healthy controls. BMC Neurol 18 (1), 67. https://doi.org/10.1186/s12883-018-1065-9.

Gabilondo, I., Martínez-Lapiscina, E.H., Fraga-Pumar, E., Ortiz-Perez, S., Torres-Torres, R., Andorra, M., Llufriu, S., Zubizarreta, I., Saiz, A., Sanchez-Dalmau, B., Villoslada, P., 2015. Dynamics of retinal injury after acute optic neuritis. Ann Neurol 77 (3), 517–528. https://doi.org/10.1002/ana.24351.

Garcia-Martin, E., Pinilla, I., Idoipe, M., Fuertes, I., Pueyo, V., 2011. Intra and interoperator reproducibility of retinal nerve fibre and macular thickness measurements using Cirrus Fourier-domain OCT. Acta Ophthalmol 89 (1), e23–e29. https://doi.org/10.1111/j.1755-3768.2010.02045.x.

García-Martín, E., Pueyo, V., Fernández, J., Martín, J., Ara, J.R., Almarcegui, C., Dolz, I., 2010. Effect of treatment in loss of retinal nerve fibre layer in multiple sclerosis patients]. Arch Soc Esp Oftalmol 85 (6), 209–214. https://doi.org/10.1016/j.oftal.2010.08.004 (Influencia del tratamiento en la pérdida de fibras nerviosas de la retina en pacientes con esclerosis múltiple.).

Gordon-Lipkin, E., Chodkowski, B., Reich, D.S., Smith, S.A., Pulicken, M., Balcer, L.J., Frohman, E.M., Cutter, G., Calabresi, P.A., 2007. Retinal nerve fiber layer is associated with brain atrophy in multiple sclerosis. Neurology 69 (16), 1603–1609. https://doi.org/10.1212/01.wnl.0000295995.46586.ae.

Graves, J.S., 2019. Optical Coherence Tomography in Multiple Sclerosis. Semin Neurol 39 (6), 711–717. https://doi.org/10.1055/s-0039-1700528.

Green, A.J., McQuaid, S., Hauser, S.L., Allen, I.V., Lyness, R., 2010. Ocular pathology in multiple sclerosis: retinal atrophy and inflammation irrespective of disease duration. Brain 133 (6), 1591–1601. https://doi.org/10.1093/brain/awq080. Pt.

Kappos, L., Bar-Or, A., Cree, B.A.C., Fox, R.J., Giovannoni, G., Gold, R., Vermersch, P., Arnold, D.L., Arnould, S., Scherz, T., Wolf, C., Wallström, E., Dahlke, F., 2018. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet 391 (10127), 1263–1273. https://doi.org/10.1016/s0140-6736(18)30475-6.

Khanifar, A.A., Parlitsis, G.J., Ehrlich, J.R., Aaker, G.D., D'Amico, D.J., Gauthier, S.A., Kiss, S., 2010. Retinal nerve fiber layer evaluation in multiple sclerosis with spectral domain optical coherence tomography. Clin Ophthalmol 4, 1007–1013. https://doi.org/10.2147/opth.s13278.

Kuchling, J., Paul, F., 2020. Visualizing the Central Nervous System: imaging Tools for Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorders. Front Neurol 11, 450. https://doi.org/10.3389/fneur.2020.00450.

Lambe, J., Saidha, S., Bermel, R.A., 2020. Optical coherence tomography and multiple sclerosis: update on clinical application and role in clinical trials. Mult Scler 26 (6), 624–639. https://doi.org/10.1177/1352458519872751.

Martinez-Lapiscina, E.H., Arnow, S., Wilson, J.A., Saidha, S., Preiningerova, J.L., Oberwahrenbrock, T., Brandt, A.U., Pablo, L.E., Guerrieri, S., Gonzalez, I., Outteryck, O., Mueller, A.K., Albrecht, P., Chan, W., Lukas, S., Balk, L.J., Fraser, C., Frederiksen, J.L., Resto, J., …Villoslada, P., 2016. Retinal thickness measured with optical coherence tomography and risk of disability worsening in multiple sclerosis: a cohort study. The Lancet Neurol. 15 (6), 574–584. https://doi.org/10.1016/s1474-4422(16)00068-5.

Mehmood, A., Ali, W., Song, S., Din, Z.U., Guo, R.Y., Shah, W., Ilahi, I., Yin, B., Yan, H., Zhang, L., Khan, M., Ali, W., Zeb, L., Safari, H., Li, B., 2021. Optical coherence tomography monitoring and diagnosing retinal changes in multiple sclerosis. Brain Behav 11 (10), e2302. https://doi.org/10.1002/brb3.2302.

Mirmosayyeb, O., Yazdan Panah, M., Mokary, Y., Ghaffary, E.M., Ghoshouni, H., Zivadinov, R., Weinstock-Guttman, B., Jakimovski, D., 2023. Optical coherence tomography (OCT) measurements and disability in multiple sclerosis (MS): a systematic review and meta-analysis. J Neurol Sci 454, 120847. https://doi.org/10.1016/j.jns.2023.120847.

Oertel, F.C., Zimmermann, H.G., Brandt, A.U., Paul, F., 2019. Novel uses of retinal imaging with optical coherence tomography in multiple sclerosis. Expert Rev Neurother 19 (1), 31–43. https://doi.org/10.1080/14737175.2019.1559051.

Parisi, V., Manni, G., Spadaro, M., Colacino, G., Restuccia, R., Marchi, S., Bucci, M.G., Pierelli, F., 1999. Correlation between morphological and functional retinal impairment in multiple sclerosis patients. Invest Ophthalmol Vis Sci 40 (11), 2520–2527. https://iovs.arvojournals.org/article.aspx?articleid=2199757.

Paul, F., Calabresi, P.A., Barkhof, F., Green, A.J., Kardon, R., Sastre-Garriga, J., Schippling, S., Vermersch, P., Saidha, S., Gerendas, B.S., Schmidt-Erfurth, U., Agoropoulou, C., Zhang, Y., Seifer, G., Petzold, A., 2021. Optical coherence tomography in multiple sclerosis: a 3-year prospective multicenter study. Ann Clin Transl Neurol 8 (12), 2235–2251. https://doi.org/10.1002/acn3.51473.

Petzold, A., Balcer, L.J., Calabresi, P.A., Costello, F., Frohman, T.C., Frohman, E.M., Martinez-Lapiscina, E.H., Green, A.J., Kardon, R., Outteryck, O., Paul, F., Schippling, S., Vermersch, P., Villoslada, P., Balk, L.J., 2017. Retinal layer segmentation in multiple sclerosis: a systematic review and meta-analysis. The Lancet Neurol. 16 (10), 797–812. https://doi.org/10.1016/s1474-4422(17)30278-8.

Pietroboni, A.M., Carandini, T., Dell'Arti, L., Bovis, F., Colombi, A., De Riz, M.A., Casazza, E., Scola, E., Fenoglio, C., Arighi, A., Fumagalli, G.G., Triulzi, F., Galimberti, D., Viola, F., Scarpini, E., 2020. Evidence of retinal anterograde neurodegeneration in the very early stages of multiple sclerosis: a longitudinal OCT study. Neurol Sci 41 (11), 3175–3183. https://doi.org/10.1007/s10072-020-04431-4.

Saidha, S., Al-Louzi, O., Ratchford, J.N., Bhargava, P., Oh, J., Newsome, S.D., Prince, J.L., Pham, D., Roy, S., van Zijl, P., Balcer, L.J., Frohman, E.M., Reich, D.S., Crainiceanu, C., Calabresi, P.A., 2015. Optical coherence tomography reflects brain atrophy in multiple sclerosis: a four-year study. Ann Neurol 78 (5), 801–813. https://doi.org/10.1002/ana.24487.

Saidha, S., Syc, S.B., Durbin, M.K., Eckstein, C., Oakley, J.D., Meyer, S.A., Conger, A., Frohman, T.C., Newsome, S., Ratchford, J.N., Frohman, E.M., Calabresi, P.A., 2011. Visual dysfunction in multiple sclerosis correlates better with optical coherence tomography derived estimates of macular ganglion cell layer thickness than peripapillary retinal nerve fiber layer thickness. Mult Scler 17 (12), 1449–1463. https://doi.org/10.1177/1352458511418630.

Schippling, S., Balk, L.J., Costello, F., Albrecht, P., Balcer, L., Calabresi, P.A., Frederiksen, J.L., Frohman, E., Green, A.J., Klistorner, A., Outteryck, O., Paul, F., Plant, G.T., Traber, G., Vermersch, P., Villoslada, P., Wolf, S., Petzold, A., 2015. Quality control for retinal OCT in multiple sclerosis: validation of the OSCAR-IB criteria. Mult Scler 21 (2), 163–170. https://doi.org/10.1177/1352458514538110.

Siger, M., Dziegielewski, K., Jasek, L., Bieniek, M., Nicpan, A., Nawrocki, J., Selmaj, K., 2008. Optical coherence tomography in multiple sclerosis: thickness of the retinal nerve fiber layer as a potential measure of axonal loss and brain atrophy. J Neurol 255 (10), 1555–1560. https://doi.org/10.1007/s00415-008-0985-5.

Swinnen, S., De Wit, D., Van Cleemput, L., Cassiman, C., Dubois, B., 2023. Optical coherence tomography as a prognostic tool for disability progression in MS: a systematic review. J Neurol 270 (2), 1178–1186. https://doi.org/10.1007/s00415-022-11474-4.

Vidal-Jordana, A., Pareto, D., Cabello, S., Alberich, M., Rio, J., Tintore, M., Auger, C., Montalban, X., Rovira, A., Sastre-Garriga, J., 2020. Optical coherence tomography measures correlate with brain and spinal cord atrophy and multiple sclerosis disease-related disability. Eur J Neurol 27 (11), 2225–2232. https://doi.org/10.1111/ene.14421.

Winges, K.M., Murchison, C.F., Bourdette, D.N., Spain, R.I., 2019. Longitudinal optical coherence tomography study of optic atrophy in secondary progressive multiple sclerosis: results from a clinical trial cohort. Mult Scler 25 (1), 55–62. https://doi.org/10.1177/1352458517739136.

World Medical Association, 2024. Declaration of Helsinki - Ethical Principles For Medical Research Involving Human Subjects. Ferney-Voltaire: Author. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/. Accessed 06 January 2025.