

## Supplemental Material

### 1. eMethods

#### Procedures

Participants completed the German version of the National Eye Institute Visual Function Questionnaire 25 (NEI-VFQ 25) at baseline and at week 26. Scores in this instrument range from 0 to 100 and higher scores indicate better vision-related quality of life. We computed the composite overall score as the unweighted average of all subscores. An ophthalmological and neurological examination was conducted at baseline and week 1, week 4, week 16, and week 26. It included measurements of high contrast visual acuity (ETDRS chart score), low contrast letter acuity (2.5% Sloan chart score), contrast sensitivity (log), visual fields, visual evoked potentials (VEP) p100 amplitudes and peak times, and the expanded disability status scale (EDSS). We performed macular (30°x25° with 61 B-Scans and 15 automatic real-time in high-speed mode) and peripapillary (3.5 mm, 4.1 mm, and 4.7 mm cirumpapillary circles) optical coherence tomography (OCT) scans at baseline, week 4, week 16, and week 26. These were evaluated in a central reading center (Bern, Switzerland). The peripapillary retinal nerve fiber layer (pRNFL) thickness was computed by manual segmentation in pre-specified sectors. For the current report, we used the RetinAI discover platform to obtain the average thickness of macular retinal layers by sector according to the ETDRS grid. These included the macular retinal nerve fiber layer (mRFNL), the combined ganglion cell and inner plexiform layer (mGCIPL), the inner nuclear layer (mINL), the combined inner plexiform and outer nuclear layer (mINOPL), the outer plexiform layer (mOPL), and the combined layers of the photoreceptors and retinal pigment epithelium (mPRRPE).

#### Statistical Analysis of VEP data

##### *Imputation*

Frequently, no reliable VEP response could be measured in cases of low vision. Affected eye measurements of the VEP P100 amplitude were available from 67 patients at baseline, 90 patients at week 4, 82 patients at week 16, and 88 patients at week 26. We imputed “0  $\mu$ V” for missing affected eye measurements in 21 cases, 6 cases, 4 cases, and 0 cases at these time points, respectively. We only imputed values if a successful measurement of the fellow, unaffected eye had been performed on the same visit.

Affected eye measurements of the VEP P100 peak time were available from 67 patients at baseline, 93 patients at week 4, 86 patients at week 16, and 90 patients at week 26. We did not perform any imputations on these data since there is no natural upper boundary for VEP peak times. We acknowledge that the time course model of these data will likely underestimate the recovery of conduction velocity, especially within the first four weeks.

##### *Justification of additional adjustment by study center*

On exploratory data analysis, we found that VEP peak time measurements of the unaffected eye were lower in one study center. We therefore included an additional adjustment for the study center in the analysis of all VEP data. Per-patient random effects in these models were nested within center effects.

## 2. Patient characteristics

**eTable 1. Pooled patient and baseline characteristics of the TONE study population.**

	Pooled patient characteristics of the TONE trial (n=103)
Age, years	30 (25 to 36)
Sex	
Female	71 (69%)
Male	32 (31%)
Study medication	
MP + Erythropoietin	52 (50%)
MP + Placebo	51 (50%)
Time from onset to treatment, days	6 (4 to 7)
Clinical presentation	
Pain on eye movements	84 (82%)
Clinical disc swelling in the affected eye	23 (23%)
Multiple Sclerosis (MS)	
Known MS at baseline	0 (0%)
Conversion to MS during follow-up	47 (38%)
Disease modifying Therapy (DMT)	
On DMT at baseline	0 (0%)
Initiated DMT during follow-up	33 (32%)
Time to initiation of DMT, days	48 (31 to 122)
EDSS	3 (2 to 3)
Antibody testing	
Aquaporin-4 antibody positive	0 (0%)
Erythropoietin antibody positive	0 (0%)
Global pRNFL thickness (3.5 mm), $\mu\text{m}$	
affected eye	114.6 (31.5)
fellow eye	100.2 (11.9)
mGCIPL thickness, $\mu\text{m}$	
affected eye	68.8 (5.3)
fellow eye	69.1 (4.8)
HCVA, ETDRS chart score	
affected eye	91 (88 to 94)
unaffected eye	44 (14 to 64)
LCLA, 2.5% Sloan Chart Score	
affected eye	0.0 (0.0 to 0.0)
fellow eye	67.0 (58.8 to 71.0)
CS, log	
affected eye	0.7 (0.2 to 1.0)
fellow eye	1.7 (1.6 to 1.8)

VF mean defect, dB	
affected eye	26.0 (15.5 to 26.0)
fellow eye	3.1 (1.5 to 4.6)
VEP P100 peak time, ms	
affected eye	125.0 (110.9 to 150.7)
fellow eye	103.0 (96.5 to 108.6)
VEP P100 amplitude, $\mu$ V	
affected eye	3.5 (0.5 to 4.8)
fellow eye	9.5 (6.7 to 14.4)

Data are n (%), median (Q1 to Q3) or mean (SD). CS=Contrast sensitivity, EDSS=Expanded disability status scale, HCVA=high contrast visual acuity, LCLA=low-contrast letter acuity, MP=Methylprednisolone, mGCIPL=Macular ganglion cell and inner plexiform layer, pRNFL=peripapillary retinal nerve fiber layer. VEP=Visual evoked potentials.

### 3. Time course of structural outcomes

#### 3.1. Change in peripapillary retinal nerve fiber layer thickness

**eTable 2. Time course of peripapillary retinal nerve fiber layer thickness (3.5 mm diameter), relative to the unaffected eye at baseline**

pRNFL sector (3.5 mm)	Baseline estimate, $\mu$ m (95% CI)	Change from baseline to week 4, $\mu$ m/week (95% CI)	Change from week 4 to week 16, $\mu$ m/week (95% CI)	Change from week 16 to week 26, $\mu$ m/week (95% CI)
Global	14.8 (9.1 to 20.5)	-2.1 (-3.3 to -0.9)	-1.7 (-2.0 to -1.3)	-0.2 (-0.3 to -0.1)
Temporal	2.3 (0.0 to 4.6)	-1.2 (-1.7 to -0.8)	-1.2 (-1.4 to -1.0)	-0.1 (-0.2 to 0.0)
Papillomacular bundle	1.7 (0.0 to 3.5)	-1.3 (-1.7 to -1.0)	-0.7 (-0.8 to -0.5)	-0.1 (-0.2 to 0.0)
Temporal superior	19.0 (10.7 to 27.3)	-2.5 (-3.9 to -1.1)	-2.2 (-2.7 to -1.7)	-0.2 (-0.3 to -0.1)
Temporal inferior	23.6 (13.7 to 33.4)	-4.1 (-6.2 to -2.1)	-2.5 (-3.1 to -1.9)	-0.2 (-0.4 to 0.0)
Nasal superior	23.7 (14.5 to 32.9)	-2.8 (-4.2 to -1.4)	-1.8 (-2.4 to -1.2)	-0.2 (-0.7 to 0.3)
Nasal inferior	25.2 (15.8 to 34.6)	-3.0 (-4.9 to -1.2)	-1.8 (-2.3 to -1.3)	-0.3 (-0.4 to -0.2)

pRNFL=Peripapillary retinal nerve fiber layer.

**eTable 3. Time course of peripapillary retinal nerve fiber layer thickness (4.1 mm diameter), relative to the unaffected eye at baseline**

pRNFL sector (4.1 mm)	Baseline estimate, $\mu$ m (95% CI)	Change from baseline to week 4, $\mu$ m/week (95% CI)	Change from week 4 to week 16, $\mu$ m/week (95% CI)	Change from week 16 to week 26, $\mu$ m/week (95% CI)
Global	8.2 (5.0 to 11.4)	-0.8 (-1.5 to -0.2)	-1.2 (-1.5 to -1.0)	-0.2 (-0.3 to -0.2)
Temporal	1.6 (-0.1 to 3.3)	-1.0 (-1.3 to -0.6)	-0.9 (-1.1 to -0.8)	-0.1 (-0.2 to 0.0)
Papillomacular bundle	1.9 (0.5 to 3.4)	-1.2 (-1.5 to -0.9)	-0.5 (-0.6 to -0.4)	-0.1 (-0.1 to 0.0)
Temporal superior	10.3 (4.9 to 15.8)	-1.0 (-1.9 to -0.2)	-1.8 (-2.2 to -1.4)	-0.2 (-0.4 to -0.1)
Temporal inferior	13.7 (7.8 to 19.6)	-1.7 (-2.7 to -0.7)	-2.0 (-2.6 to -1.5)	-0.3 (-0.7 to 0.1)
Nasal superior	13.2 (7.6 to 18.8)	-0.9 (-1.9 to 0.2)	-1.2 (-1.6 to -0.8)	-0.3 (-0.5 to -0.2)
Nasal inferior	13.7 (7.8 to 19.5)	-1.1 (-2.0 to -0.3)	-1.2 (-1.6 to -0.8)	-0.2 (-0.6 to 0.1)

pRNFL=Peripapillary retinal nerve fiber layer.

**eTable 4. Time course of peripapillary retinal nerve fiber layer thickness (4.7 mm diameter), relative to the unaffected eye at baseline**

pRNFL sector (4.7 mm)	Baseline estimate, $\mu\text{m}$ (95% CI)	Change from baseline to week 4, $\mu\text{m}/\text{week}$ (95% CI)	Change from week 4 to week 16, $\mu\text{m}/\text{week}$ (95% CI)	Change from week 16 to week 26, $\mu\text{m}/\text{week}$ (95% CI)
Global	4.8 (3.0 to 6.6)	-0.2 (-0.6 to 0.2)	-1.0 (-1.2 to -0.8)	-0.2 (-0.3 to -0.1)
Temporal	1.8 (0.4 to 3.2)	-1.0 (-1.2 to -0.7)	-0.7 (-0.9 to -0.6)	-0.1 (-0.1 to 0.0)
Papillomacular bundle	2.4 (0.9 to 3.8)	-1.3 (-1.5 to -1.0)	-0.3 (-0.4 to -0.2)	0.0 (-0.1 to 0.0)
Temporal superior	5.9 (2.1 to 9.7)	-0.5 (-1.0 to 0.0)	-1.4 (-1.7 to -1.1)	-0.2 (-0.4 to 0.0)
Temporal inferior	7.6 (3.5 to 11.6)	-0.7 (-1.4 to 0.1)	-1.6 (-2.0 to -1.3)	-0.3 (-0.4 to -0.1)
Nasal superior	6.7 (3.7 to 9.7)	0.3 (-0.2 to 0.8)	-0.9 (-1.2 to -0.7)	-0.2 (-0.4 to 0.0)
Nasal inferior	7.1 (3.9 to 10.3)	0.0 (-0.5 to 0.5)	-0.8 (-1.1 to -0.6)	-0.3 (-0.5 to -0.1)

pRNFL=Peripapillary retinal nerve fiber layer.

### 3.2. Change in macular retinal layer thickness

**eTable 5. Time course of macular retinal layer thickness changes**

Macular retinal layer (6 mm ETDRS grid)	Change of mean thickness from baseline to week 4, $\mu\text{m}/\text{week}$ (95% CI)	Change of mean thickness from week 4 to week 16, $\mu\text{m}/\text{week}$ (95% CI)	Change of mean thickness from week 16 to week 26, $\mu\text{m}/\text{week}$ (95% CI)
RNFL	-0.7 (-0.8 to -0.5)	-0.3 (-0.4 to -0.2)	0.0 (-0.1 to 0.0)
GCIPL	-1.5 (-1.7 to -1.3)	-0.2 (-0.3 to -0.2)	0.0 (0.0 to 0.0)
INOPL	0.1 (0.1 to 0.2)	-0.1 (-0.1 to -0.1)	0.0 (0.0 to 0.0)
ONL	0.7 (0.6 to 0.9)	-0.1 (-0.1 to -0.1)	-0.1 (-0.1 to -0.1)
PRRPE	0.1 (0.0 to 0.2)	0.1 (0.0 to 0.1)	0.0 (-0.1 to 0.0)

ETDRS=Early Treatment of Diabetic Retinopathy Study, RNFL=Retinal nerve fiber layer, GCIPL=Ganglion cell and inner plexiform layer, INOPL=Inner nuclear and outer plexiform layer, ONL=Outer nuclear layer, PRRPE=Photoreceptor and retinal pigment epithelium.

## 4. Time course of functional outcomes

**eTable 6. Time course of functional outcomes**

Outcome	Baseline estimate (95% CI)	Change/week from baseline to week 4 (95% CI)	Change/week from week 4 to week 16 (95% CI)	Change/week from week 16 to week 26 (95% CI)
HCVA, ETDRS chart score	39.2 (34.0 to 44.4)	10.1 (8.7 to 11.6)	0.3 (0.1 to 0.4)	0.1 (0.0 to 0.3)
LCLA, 2.5% Sloan chart score	2.8 (0.8 to 4.8)	8.4 (7.1 to 9.5)	0.7 (0.4 to 1.0)	0.4 (0.1 to 0.6)
CS, log	0.61 (0.52 to 0.71)	0.19 (0.17 to 0.22)	0.01 (0.01 to 0.2)	0.00 (0.00 to 0.01)
VF mean defect, dB	19.6 (18.0 to 21.1)	-3.3 (-3.7 to -2.9)	-0.2 (-0.2 to -0.1)	-0.1 (-0.1 to 0.0)
VEP P100 amplitude*, $\mu$ V	3.13 (2.15 to 4.11)	1.14 (0.89 to 1.39)	0.10 (0.03 to 0.16)	0.07 (-0.00 to 0.14)
VEP P100 peak time*, ms	124.7 (117.6 to 131.7)	0.9 (-0.6 to 2.3)	-0.4 (-0.6 to -0.1)	-0.4 (-0.8 to -0.1)

HCVA=High contrast visual acuity, ETDRS=Early Treatment of Diabetic Retinopathy Study, LCLA=Low contrast letter acuity, CS=Contrast sensitivity, VEP=Visual evoked potentials. \*=model with additional adjustment for center effects

## 5. List of eFigures

### **eFigure 1. Time course of peripapillary nerve fiber layer thickness changes, by sectors.**

The per cent relative change compared to the unaffected eye at baseline is shown per sector as a color gradient ranging from red (thinning) to white (no change) to blue (thickening). Relative changes are depicted in the circumpapillary 3.5 mm, 4.1 mm, and 4.7 mm circles. The sectors are, starting from the top-left: Nasal superior, Temporal superior, Temporal, Temporal Inferior, Nasal inferior. The central circle depicts the global thickness. The inset in the temporal sector depicts the thickness in the papillomacular bundle. pRNFL=Peripapillary retinal nerve fiber layer.

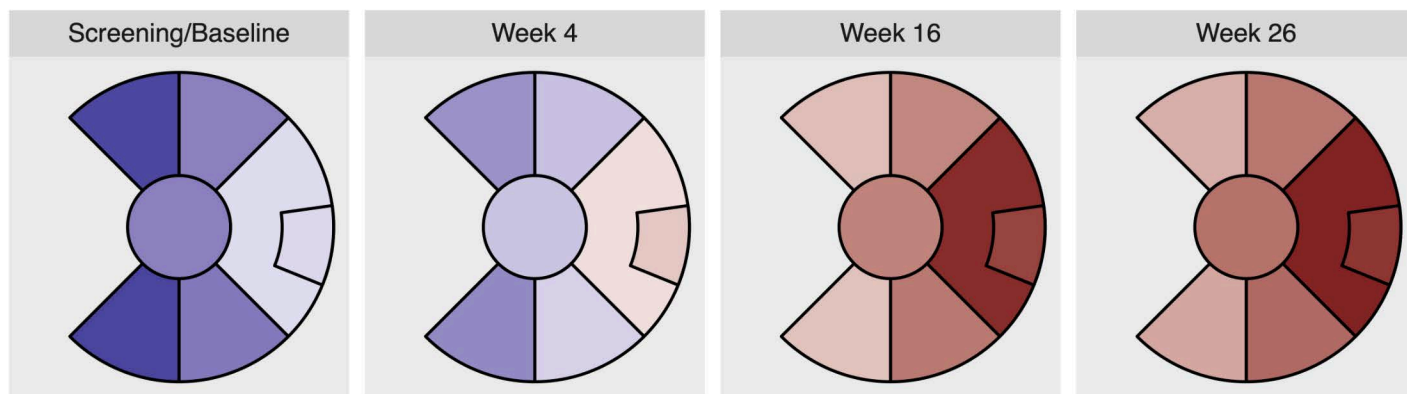
### **eFigure 2. Time course of macular retinal layer thickness changes, per ETDRS sector.**

The per cent relative change compared to the affected eye at baseline is shown per sector as a color gradient ranging from red (thinning) to white (no change) to blue (thickening). Relative changes in macular retinal layer thicknesses. Sectors are in the ETDRS grid with 1mm, 3 mm, and 6 mm diameters. T=Temporal. S=Superior. I=Inferior. N=Nasal. RPE=Retinal pigment epithelium.

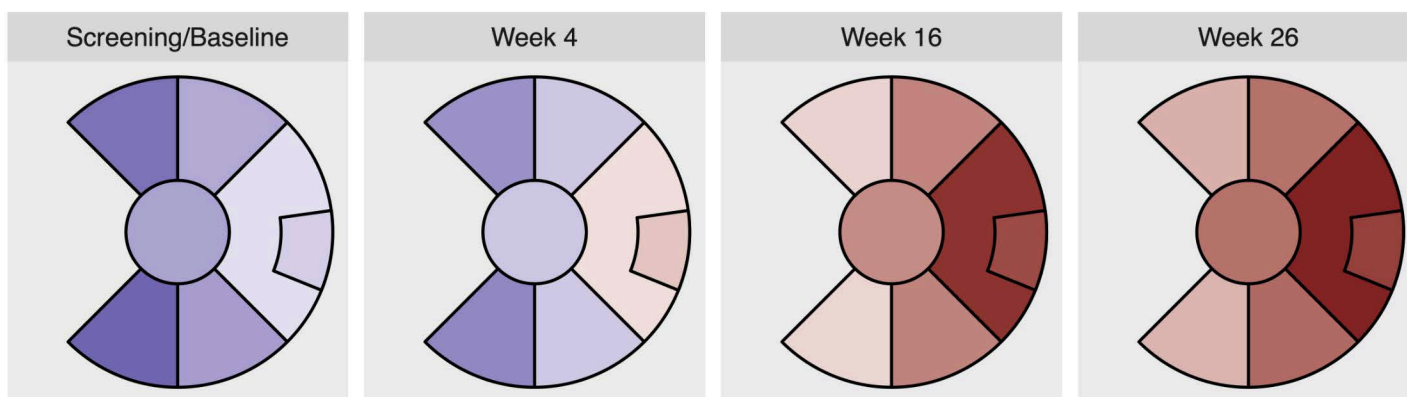
**eFigure 3. Time course of contrast sensitivity.** Triangles are individual data points. Thick black lines are estimated population means. CS=Contrast sensitivity.

**eFigure 4. Time course of the visual field mean defect.** Triangles are individual data points. Thick black lines are estimated population means.

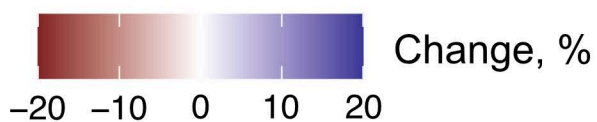
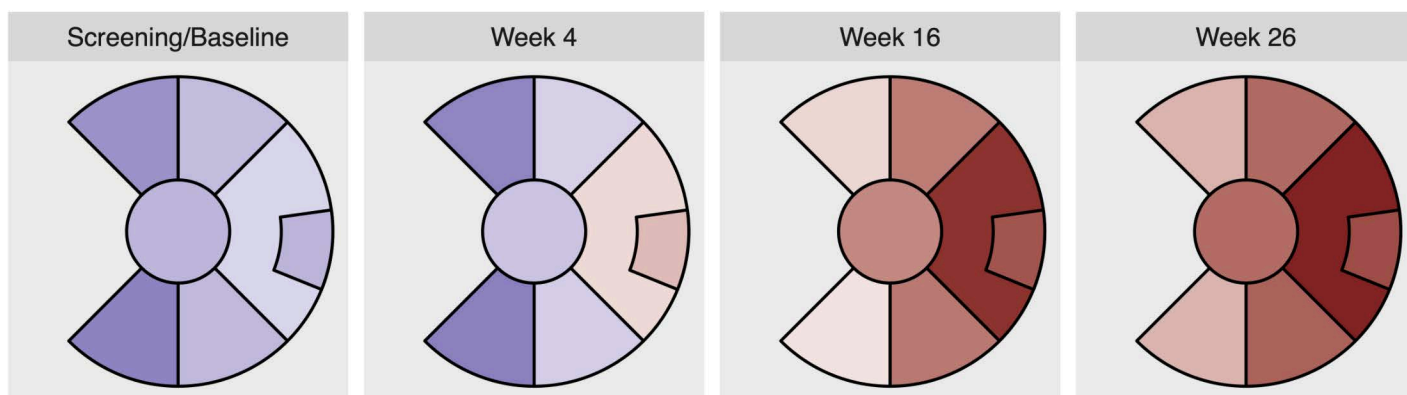
pRNFL thickness, 3.5 mm circle



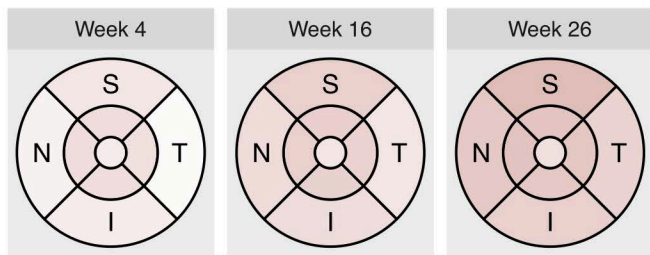
pRNFL thickness, 4.1 mm circle



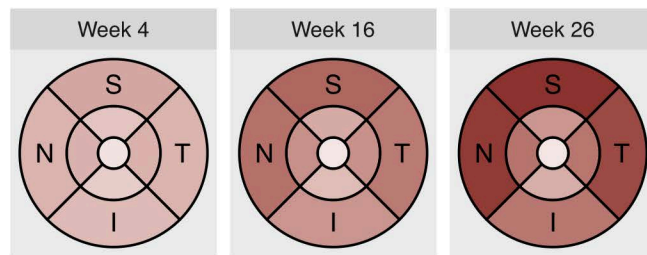
pRNFL thickness, 4.7 mm circle



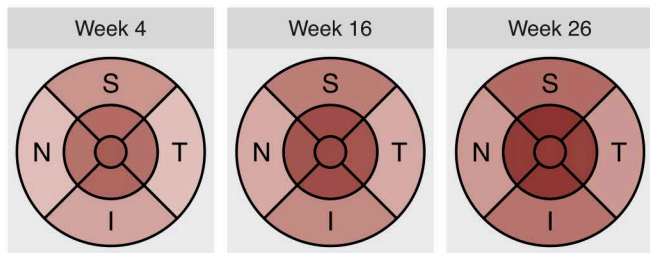
Macular total retinal thickness



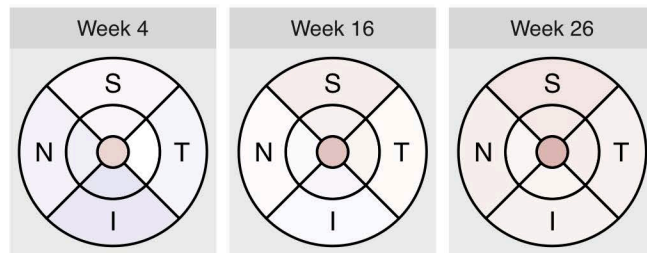
Macular retinal nerve fiber layer thickness



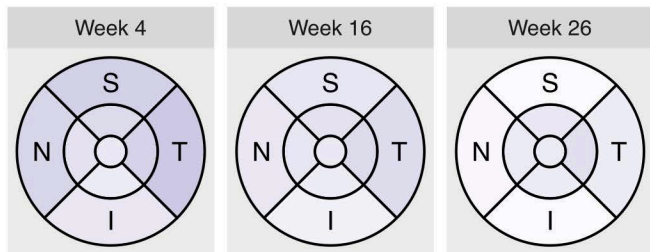
Macular ganglion cell and inner plexiform layer thickness



Macular inner nuclear and outer plexiform layer thickness



Macular outer nuclear layer thickness



Macular photoreceptor layer and RPE thickness

