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Initial Impairment and Recovery of Vision-Related Functioning in Participants With Acute Optic Neuritis From the RENEW Trial of Opicinumab

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Background: Leucine-rich repeat and immunoglobulin domain-containing Nogo receptor-interacting protein 1 (LINGO-1) is a key suppressor of oligodendrocyte differentiation and axonal remyelination and regeneration. This analysis evaluated the potential benefit of opicinumab, a human monoclonal antibody against LINGO-1, vs placebo on exploratory clinical endpoints of patient-reported vision-related functioning and high-contrast visual acuity (HCVA) in RENEW participants with acute optic neuritis (AON).
Methods: Participants were randomized to 100 mg/kg opicinumab intravenous or placebo every 4 weeks (6 infusions). Assessments were conducted in the per-protocol (PP) population and included: 25-item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25), 10-item Neuro-Ophthalmic Supplement (NOS-10), and HCVA.

Results: The opicinumab group (n = 33) had worse mean (SD) baseline patient-reported vision-related functioning scores vs placebo (n = 36): NEI-VFQ-25 composite, 75.5 (17.6) vs 79.0 (16.6); NOS-10 composite, 63.6 (19.8) vs 69.8 (21.2), respectively. By Week 24, the placebo and opicinumab groups experienced substantial mean improvements from baseline (NEI-VFQ-25 composite, 15.17 vs 13.51 [difference (95% CI): −1.66 (−5.11 to 1.78)]; NOS-10 composite, 17.40 vs 16.04 [difference (95% CI): −1.35 (−7.38 to 4.67)]). Between-treatment differences in mean change from baseline were not significantly different at any time point. Analysis of covariance–adjusted mean recovery from baseline in HCVA at Week 24 for the affected eyes was 11.8 and 8.7 letters for placebo and opicinumab, respectively ($P = 0.202$).
Conclusions: Most participants in the RENEW PP population demonstrated substantial recovery from baseline in patient-reported vision-related functioning and HCVA, regardless of treatment and structural damage. Average scores after recovery remained lower than those of published disease-free control groups. These results provide important information on visual function recovery in patients with AON, as measured by NEI-VFQ-25 and NOS-10.

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Acute optic neuritis (AON) causes permanent structural and functional optic nerve changes that may result in permanent visual impairment for some patients (1). Patients often have "good" recovery of visual acuity (VA) after AON, but deficits in patient-reported vision-related functioning, some potentially due to chronic demyelination, may remain (2–4). There are currently no established patient-reported outcome (PRO) measures specific to AON or to measure treatment benefits of central nervous system (CNS) remyelination. The 25-item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25) (5) and the 10-item Neuro-Ophthalmic Supplement

(NOS-10) (6) measure general patient-reported vision-related functioning and have been used to evaluate patients with AON and other neuro-ophthalmologic conditions (7).

Opicinumab, a human monoclonal antibody against leucine-rich repeat and immunoglobulin domain-containing Nogo receptor-interacting protein 1 (LINGO-1), is being investigated as a potential CNS remyelinating and neuroaxonal protective reparative agent for multiple sclerosis (MS) (8,9). Opicinumab blocks LINGO-1, a key suppressor of remyelination, oligodendrocyte differentiation, and regeneration of axons (9). The Phase 2a, randomized, double-blind, placebo-controlled RENEW trial examined the efficacy, safety, and pharmacokinetics of opicinumab in healthy adults with a first episode of unilateral AON (10). The opicinumab-treated group demonstrated improved recovery of conduction latency, measured by full-field visual evoked potential (FF-VEP), vs placebo at Weeks 24 (primary efficacy endpoint; $P = 0.050$) and 32 ($P = 0.011$) in the per-protocol (PP) population but not by intent-to-treat (ITT) analysis. Opicinumab was generally well tolerated, and overall incidence and severity of adverse events between treatment groups were comparable (10). This analysis evaluated the potential benefit of opicinumab vs placebo on the clinical exploratory endpoints of patient-reported vision-related functioning as measured by the NEI-VFQ-25, the NOS-10, and high-contrast VA (HCVA) in the RENEW study.

METHODS

Study Design and Participants

Full details of the RENEW trial design have been previously published (10). Eligible participants were 18–55 years of age, had no history of MS, and had a confirmed diagnosis of first episode of AON within 28 days of study baseline and a normal fellow (unaffected) eye. Patients newly diagnosed with MS because of the recent episode of AON and MRI lesions consistent with MS were eligible to participate in the RENEW study. All participants were treated with 1.0 g methylprednisolone/day intravenous (IV) for 3–5 days before randomization. Participants were randomized within 28 days of the first symptom onset to IV infusions of opicinumab (100 mg/kg) or placebo every 4 weeks from study baseline to Week 20 (for a total of 6 treatments) and followed up to Week 32. All participants provided written informed consent. The study was conducted according to the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. Before the study start, investigators obtained approval from their local ethics committee (10).

The NEI-VFQ-25, including 13 appendix items (11), and NOS-10 (both exploratory endpoints in the RENEW study), were administered using paper and pencil at screening, baseline, and Weeks 4, 8, 12, 16, 20, 24, and 32. Responses for each item are converted to a 0–100 score and computed by subscale and composite score, in which higher scores represent better visual functioning than lower scores (score of 100 reflects no impairment) (1,5). A change of $\geq$4 points was considered clinically meaningful for the NEI-VFQ-25 composite score (12). Additional background details for the NEI-VFQ-25 and NOS-10 are provided (see **Supplemental Digital Content**, Appendix E1, http://links.lww.com/WNO/A346). HCVA and low-contrast letter acuity (LCLA) were collected at the same time points. HCVA was determined by 100% contrast Sloan letter chart at 3 m, assessed individually for both eyes. The charts, provided by the sponsor and used under the standardized testing protocol, were backlit, lighting was controlled, and refraction was performed. LCLA was measured using 1.25% and 2.5% low-contrast Sloan letter charts; details of LCLA assessments have been previously described (10).

Statistical Analyses

The ITT population was defined as all randomized participants who received $\geq$1 dose of study treatment. The PP population was defined as participants who completed the study, did not miss >1 dose of treatment, and did not receive MS-modifying therapy, which was prohibited.

Between-treatment differences in mean change from baseline to Week 24 for each of the assessments were analyzed using analysis of covariance (ANCOVA). Between-treatment differences in mean change from baseline over time were analyzed using mixed-effect model repeated measure (MMRM). Models were adjusted for baseline NEI-VFQ-25 composite and NOS-10 composite scores. Last observation carried forward was used to impute missing data at Week 24 in the ANCOVA. Stability, improvement, and decline in the NEI-VFQ-25 composite score were evaluated according to percentage of participants sustaining within 4 points, improving $\geq$4 points, or declining $\geq$4 points from baseline to Week 24.

Change in the HCVA letter score of the affected eye from its own baseline to Week 24 was analyzed using ANCOVA, adjusted for the baseline HCVA. Changes in the HCVA letter score of the affected eye over time from its own baseline were analyzed using the MMRM, adjusted for baseline HCVA.

Pairwise correlation analyses were conducted from baseline to Weeks 24 and 32. Patient-reported visual function outcomes were correlated with measures of retinal structure (retinal nerve fiber layer [RNFL] thickness measured by spectral-domain optical coherence tomography [SD-OCT]) and visual pathway electrophysiological function (FF-VEP P100 amplitude and latency), as assessed in the RENEW study (10). Correlation analyses were also conducted between the change from baseline to Weeks 24 and 32 in VA outcomes (HCVA and LCLA)

and measures of retinal structural and electrophysiological function, and patient-reported visual function outcomes. Change in FF-VEP, RNFL thickness, HCVA, and LCLA for each time point is the change for the affected eye at that time point from the baseline of the unaffected fellow eye. Pearson correlation coefficients were calculated for all correlations.

RESULTS

Randomized Participants

Of the 82 participants in the ITT population, a total of 69 were included in the PP population and received either placebo (n = 36) or opicinumab (n = 33) (10). Baseline data for the PP population have been published and were similar to the ITT population (10). Briefly, in the PP population, for the placebo and opicinumab groups, respectively, 75% and 64% were women and the mean (SD) age was 32.2 (8.8) and 31.2 (7.1) years; 97% of participants in each group were Caucasian. The mean (SD) number of days from first AON symptom to first study dose was 24.3 (3.5) in the placebo group and 24.0 (3.8) in the opicinumab group. The median (range) number of days between completion of methylprednisolone treatment and date of first study dose was 13.0 (2–25) days in the placebo group and 15.0 (5–25) days in the opicinumab group (ITT population). Baseline characteristics were balanced overall between the 2 treatment groups except that a greater number of participants with more severe AON were randomized to opicinumab. More patients with FF-VEP conduction block at baseline were randomized to the opicinumab group vs placebo group (24% vs 12%, respectively), and more opicinumab-treated participants had a visual field defect, Uhthoff's symptom, and swollen optic disc at screening or baseline (10).

NEI-VFQ-25 and NOS-10 Outcomes: Per-Protocol Population

NEI-VFQ-25 composite, NOS-10 composite, and combined NEI-VFQ-25 and NOS-10 composite scores reflected impairment in patient-reported vision-related functioning in both treatment groups at baseline. The baseline mean NEI-VFQ-25 composite score was 79.0 in the placebo group and 75.5 in the opicinumab group (see **Supplemental Digital Content**, Table E1, http://links.lww.com/WNO/A323). Participants randomized to opicinumab had slightly worse scores at baseline than those randomized to placebo. Both the placebo and opicinumab groups experienced substantial improvements from baseline in NEI-VFQ-25 composite, NOS-10 composite, and combined NEI-VFQ-25 and NOS-10 composite scores by Week 24 at the end of the treatment period. These improvements were sustained at the end of the study at Week 32 (see **Supplemental Digital Content**, Table E1, http://links.lww.com/WNO/A323). However, mean final scores at recovery (Week 32; see **Supplemental Digital Content**, Table E1, http://links.lww.com/WNO/A323) remained lower than those for published disease-free control groups (reported by Sabadia et al as mean [SD] NEI-VFQ-25 composite score: 98.2 [2.1] and mean [SD] NOS-10 composite score: 96.4 [5.2]) (3).

Based on ANCOVA models, mean change from baseline to Week 24 for NEI-VFQ-25 composite, NOS-10 composite, and combined NEI-VFQ-25 and NOS-10 composite scores did not statistically differ between treatment groups, but greater numerical improvements were observed with placebo (Table 1). Between-treatment differences in mean change from baseline for the NEI-VFQ-25 composite, NOS-10 composite, and combined NEI-VFQ-25 and NOS-10 composite scores were not significantly different

TABLE 1. Change from baseline in the mean NEI-VFQ-25 composite, NOS-10 composite, and combined NEI-VFQ-25 and NOS-10 composite scores at Week 24 analyzed using ANCOVA[a] (PP population)

	Placebo (n = 36)	Opicinumab (n = 33)
NEI-VFQ-25 composite score		
Mean change from baseline	15.17	13.51
Difference with placebo (95% CI)		−1.66 (−5.11 to 1.78)
P value		0.337
NOS-10 composite score		
Mean change from baseline	17.40	16.04
Difference with placebo (95% CI)		−1.35 (−7.38 to 4.67)
P value		0.655
Combined NEI-VFQ-25 and NOS-10 composite score		
Mean change from baseline	15.83	14.88
Difference with placebo (95% CI)		−0.95 (−5.08 to 3.19)
P value		0.649

ANCOVA, analysis of covariance; NEI-VFQ-25, 25-item National Eye Institute Visual Functioning Questionnaire; NOS-10, 10-item Neuro-Ophthalmic Supplement; PP, per protocol.
[a]ANCOVA adjusted for baseline vision-related functioning assessment value.

by treatment at any time point when analyzed using the MMRM (Fig. 1).

At Week 24, most participants in both groups (placebo, 74% [26/35]; opicinumab, 69% [22/32]) had a clinically meaningful improvement of ≥4 points from baseline in NEI-VFQ-25 composite score, whereas no participants in the placebo group and 6% (2/32) of the opicinumab group experienced a ≥4-point decline (see **Supplemental Digital Content**, Figure E1, http://links.lww.com/WNO/A330). Similarly, at Week 32, 71% (25/35) and 74% (23/31) of the placebo and opicinumab groups, respectively, had a ≥4-point improvement in NEI-VFQ-25 composite score, whereas 1 participant in each group experienced a ≥4-point decline. Neither of the 2 participants who experienced the 4-point decline developed new or recurrent AON during the RENEW study.

High-Contrast Visual Acuity Outcomes: Per-Protocol Population

The mean baseline HCVA letter score of the affected eyes was lower than that of the fellow eyes in both the placebo (affected eye, 44.4 letters; fellow eye, 58.3 letters) and opicinumab groups (affected eye, 43.0 letters; fellow eye, 60.4 letters; see **Supplemental Digital Content**, Table E2, http://links.lww.com/WNO/A324). Both groups experienced partial recovery in HCVA during the study. No differences in recovery between treatment groups were observed for the ANCOVA or MMRM analyses. The adjusted mean recovery from baseline in the HCVA letter score at Week 24 for the affected eyes by ANCOVA was 11.8 letters for the placebo group and 8.7 letters for the opicinumab group (difference for the adjusted mean [95% CI]: −3.2 [–8.0 to 1.7] letters; P = 0.202). Adjusted mean changes in HVCA over time, analyzed using the MMRM, showed similar improvements in the affected eye in both treatment groups over 24 weeks (Fig. 2). In the fellow eyes, small improvements from baseline in the HCVA letter score were observed in both treatment groups (Fig. 2).

Mean LCLA outcomes at baseline and Weeks 24 and 32 for participants in the PP population of RENEW were calculated (see **Supplemental Digital Content**, Table E3, http://links.lww.com/WNO/A325). As previously described, no treatment differences were observed between placebo and opicinumab (10).

Pairwise Correlation Analyses

Results of pairwise correlation analyses are provided (see **Supplemental Digital Content**, Tables E4, http://links.lww.com/WNO/A326, E5, http://links.lww.com/WNO/A327, and E6, http://links.lww.com/WNO/A328). Change in FF-VEP, RNFL thickness, HCVA, and LCLA for each time point is the change for the affected eye at that time point from the baseline of the unaffected fellow eye. Overall, in the RENEW PP population, correlations between

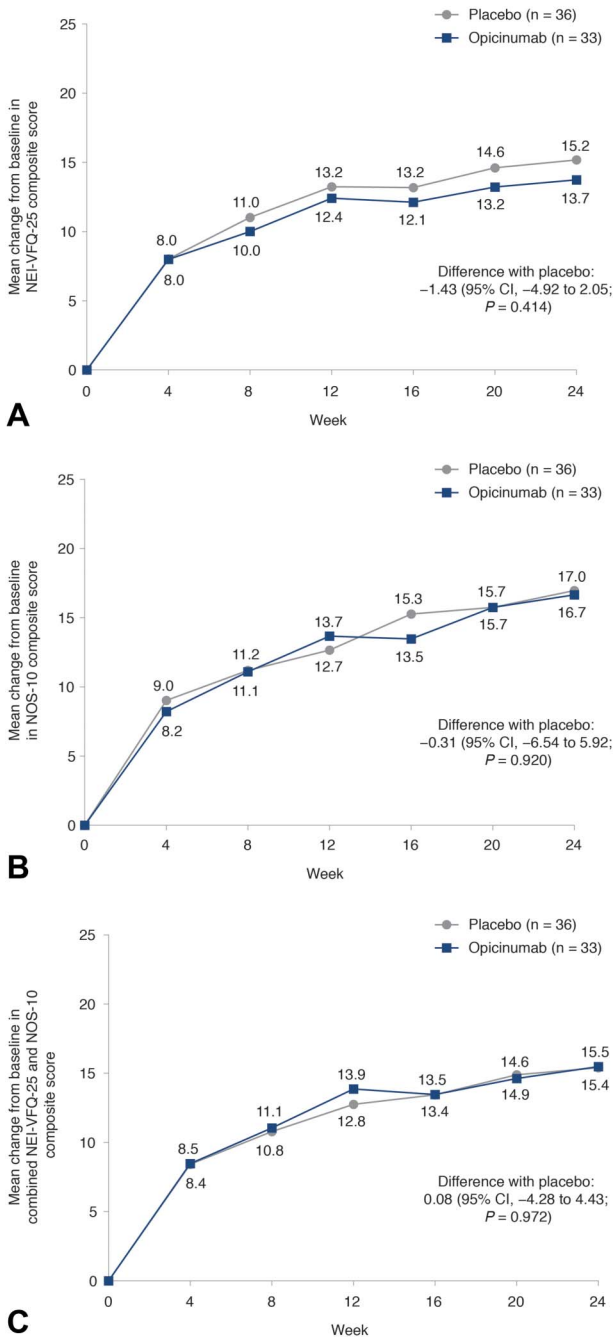

FIG. 1. Mean change from baseline to Week 24 in: (**A**) 25-item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25) composite, (**B**) 10-item Neuro-Ophthalmic Supplement (NOS-10) composite, and (**C**) combined NEI-VFQ-25 and NOS-10 composite scores analyzed using mixed-effect model repeated measure in the per-protocol population.

change from baseline in the mean NEI-VFQ-25 composite score and mean RNFL thickness and mean FF-VEP amplitude were negative and mild in both treatment groups for both time points (see **Supplemental Digital Content**, Table E4, http://links.lww.com/WNO/A326). Correlations

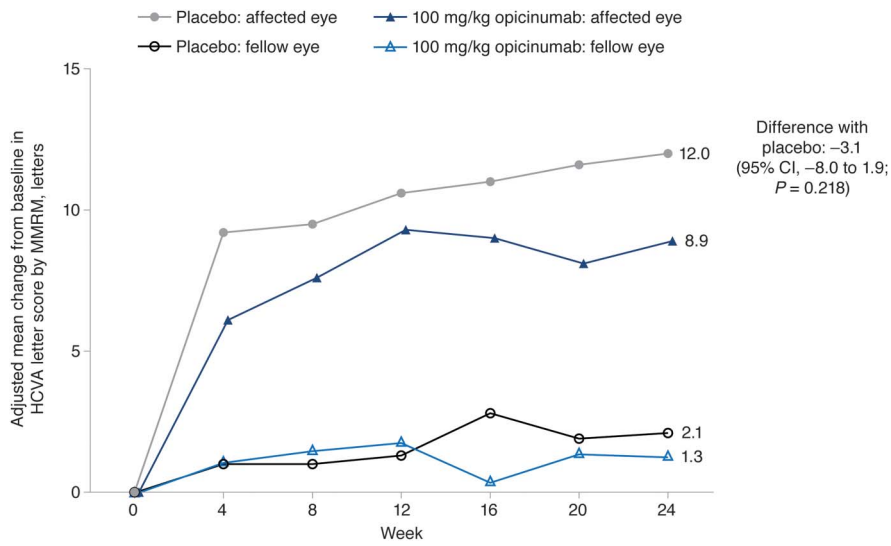

FIG. 2. Change in the high-contrast visual acuity (HCVA) letter score (affected and fellow eyes). Change from baseline in the mean HCVA letter score for affected and fellow eyes by visit analyzed using mixed-effect model repeated measure (MMRM) in the per-protocol population.

between change from baseline in the mean NEI-VFQ-25 composite score and mean FF-VEP latency were positive and mild in both treatment groups for both time points (see **Supplemental Digital Content**, Table E4, http://links.lww.com/WNO/A326). Correlations of change from baseline were largely absent between the NOS-10 composite score and RNFL thickness, FF-VEP amplitude, and FF-VEP latency for both time points and both treatment groups.

Moderate correlations were observed between recovery of HCVA and LCLA and recovery of mean FF-VEP latency in the placebo arm; this correlation was lost in the 100 mg/kg opicinumab group. RNFL thinning showed the best overall correlation with changes in LCLA in both treatment groups (see **Supplemental Digital Content**, Tables E5, http://links.lww.com/WNO/A327, and E6, http://links.lww.com/WNO/A328). Recovery of patient-reported visual function showed absent or mild correlation with changes in VA. The strongest correlation of change from baseline was observed between the 1.25% and 2.5% LCLA endpoints. HCVA was more highly correlated with 2.5% LCLA vs 1.25% LCLA.

DISCUSSION

RENEW was the first study of its kind to evaluate patient-reported visual functioning in patients with an AON episode treated with a candidate optic nerve reparative treatment in addition to the standard-of-care treatment with high-dose steroids. Randomization was balanced except that more severe cases of AON were randomized to the opicinumab group vs the placebo group, as previously discussed (10). Lower baseline NEI-VFQ-25 composite scores, NOS-10 composite scores, and lower HCVA in the affected eye (vs the fellow eye) show that most participants had some impairment in visual functioning at the start of the study. Regardless of treatment group, participants demonstrated notable improvements in patient-reported vision-related functioning scores from baseline to Week 24. In fact, most participants in both treatment groups (~70%) demonstrated a clinically meaningful improvement of ≥4 points in the NEI-VFQ-25 composite score from baseline to Week 24. Although mean NEI-VFQ-25 composite scores had substantial improvements by Week 24, they were still lower than those observed in a healthy eye disease-free reference population (3,6). These findings suggest that the participants had clinically meaningful recovery of their self-reported visual functioning but with some residual impairment resulting from persistent injury to the optic nerve and retinal ganglion cells.

Improvements in the HCVA letter score from baseline to Week 24 in the affected eye were also similar between the 2 treatment groups. Most improvements in HCVA from baseline occurred by Week 12 for both treatment groups. This observation is consistent with the natural recovery of AON, during which HCVA improves for most patients within the first 2 months after the onset of symptoms (13). Improvements from baseline in LCLA (1.25% and 2.5% Sloan chart) in the affected eye were also similar between the placebo and opicinumab groups; no between-treatment differences were observed (10). Compared with the fellow eye, deficits in LCLA were evident in the affected eye in both treatment groups at Weeks 24 and 32.

The small improvements seen in the HCVA of the fellow eyes may be due to practice effects and familiarity with standardized testing conditions, as the tests were repeated frequently over 24 weeks. However, subtle involvement of the fellow eye in cases of unilateral AON

has been suggested as another possible mechanism. An analysis of fellow eyes in patients from the Optic Neuritis Treatment Trial (ONTT) reported that visual deficits observed in the fellow eye of some patients at the onset of unilateral AON recovered to normal after 6 months and may not have been related to preexisting demyelination (14).

Changes in RFNL thickness, P100 latency, and P100 amplitude were found to be weakly correlated with change in patient-reported visual function as measured with the NEI-VFQ-25, but no correlations were observed with the NOS-10. Changes in VA outcomes demonstrated no correlations with changes in the NEI-VFQ-25 and mild to absent correlations with changes in the NOS-10. The strongest correlations between change in VA and biomarkers were seen for P100 latency and LCLA in the placebo arm. By contrast, a mild correlation was seen for change in VA with change in P100 amplitude in the opicinumab group but not in the placebo group. Change in RNFL thickness showed a consistent correlation with the change from baseline in all LCLA outcomes in both the placebo and opicinumab groups, linking RNFL thickness to LCLA. Treatment with opicinumab improved the latency without corresponding improvements in measures of VA.

Despite the marked improvements from baseline in the affected eyes, the HCVA of the affected eyes remained below that of the fellow eyes in both treatment groups. Previous studies have shown that patient-reported vision-related functioning is reduced in patients with a history of AON even with "good" recovery of HCVA. An analysis of patients from the ONTT found that NEI-VFQ-25 scores were lower in study patients compared with an independent healthy reference group 5–8 years after study entry, despite the majority of patients (61%) having VA 20/20 or better (1). A cross-sectional observational cohort study by Sabadia et al (3) that examined patient-reported vision-related functioning in patients with history of AON with VA recovery of 20/40 or better also found that NEI-VFQ-25 and NOS-10 scores were significantly reduced compared with disease-free controls.

The residual impairment in patient-reported visual functioning, HCVA, and LCLA seen in some participants is consistent with the SD-OCT–observed retinal ganglion cell layer neuronal thinning that occurred early after the AON onset and was completed to a large extent before study randomization (10). This limited the ability to study whether treatment with opicinumab may be neuroprotective when given within 28 days of the onset of AON, suggesting a shorter enrollment window than that used in the RENEW study may be needed in future studies of neuroprotective therapies.

The marked and natural recovery of patient-reported visual functioning scores and HCVA in the placebo group of patients with AON further limited the potential to demonstrate the clinical benefit of opicinumab in the RENEW study. The simple activities assessed with these measures may not adequately capture the complex multidimensional activities used by subjects in this population affected by AON and at risk of AON episodes. Presently, the only therapy available for the treatment of AON is a short course of high-dose IV steroids, such as methylprednisolone, which may accelerate recovery of vision but does not significantly improve long-term visual function (13). It is possible that administration of methylprednisolone played some role in the clinical recovery observed in both arms of this study (13).

It is unclear whether any of the 49 items included in the NEI-VFQ-25 and NOS-10 are specifically sensitive to demyelination/remyelination in the optic nerve, as these instruments are not specific to AON. The NOS-10, which was developed for neuro-ophthalmologic disorders (6), seems to be more sensitive than the NEI-VFQ-25 based on the nature of its items and the lower baseline and end of study scores. In this study, it showed more impairment at baseline and had more sensitivity to change over time than the NEI-VFQ-25. However, the change in NEI-VFQ-25 scores showed some correlation with changes by OCT and VEP, whereas the NOS-10 did not. In addition, neither item sets are specific to the sudden loss of vision because of AON or the complex daily visual activities in an otherwise healthy, working-age population.

It is important to understand the mechanisms underlying the observed recovery in vision-related PROs in the placebo group from baseline to Week 24. The mandatory use of high-dose steroids likely contributed to the speed of visual recovery (13). The fact that participants similarly recovered on VA scores regardless of VEP latency recovery is a critical issue to examine in the context of the clinical development of CNS remyelinating therapies and the observed benefit of opicinumab on VEP latency recovery in the PP population (10). VEP latency recovery was selected as the primary efficacy endpoint in the RENEW study because it was predicted to be the most sensitive to a CNS remyelinating therapy and because CNS remyelination had the strongest evidence of efficacy in preclinical rodent models. At present, there is no clarity on which clinical measures, if any, are sensitive to CNS remyelination, as this is a new therapeutic field.

Despite good recovery of HCVA and LCLA in the RENEW study, complete recovery of patient-reported visual function did not occur in many patients, likely due to the initial neuroaxonal loss as a result of AON and the persistence of demyelination for surviving optic nerve axons (4,15). The marked clinical improvement that follows AON despite residual damage to the retina and optic nerve as demonstrated by OCT and VEP may be potentially due to adaptive neuroplasticity, defined as the reorganization of the structure and function of the brain in response to

injury (16). Adaptive neuroplasticity has been proposed as a potential key contributor to the recovery of visual function in AON cases (17–19) and evidence of it in AON has been demonstrated in several studies (18–20).

Limitations of this study include the small sample size (10) and, as previously discussed, the rapid onset of injury to the retina after AON, which limited the therapeutic window for potential neuroprotection with high-dose opicinumab. Another potential limitation is that it is unclear whether the visual function endpoints selected correlate with VEP latency improvement, the prespecified primary endpoint of the RENEW study (21). Furthermore, it is possible that the current patient-reported assessments of visual functioning are mistargeted in terms of complexity and may not address important visual function items in this digitally engaged population. No qualitative or conceptual framework evidence exists to support the use of these measures in AON. Detection of movement is one example of an important visual function that is not properly captured with the existing instruments (22).

Overall, this study found that the majority of RENEW participants demonstrated improved, albeit incomplete, recovery in patient-reported visual functioning and HCVA regardless of treatment group. Despite the lack of between-treatment differences between high-dose opicinumab and placebo, these results provide important information on the course and extent of recovery of clinical visual function in patients with AON and how they relate to the structural changes that take place in the retina and optic nerve.

STATEMENT OF AUTHORSHIP

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