Safety and efficacy of opicinumab in acute optic neuritis (RENEW): a randomised, placebo-controlled, phase 2 trial

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Summary

Background The human monoclonal antibody opicinumab (BIIB033, anti-LINGO-1) has shown remyelinating activity in preclinical studies. We therefore assessed the safety and tolerability, and efficacy of opicinumab given soon after a first acute optic neuritis episode.

Methods This randomised, double-blind, placebo-controlled, phase 2 study (RENEW) was done at 33 sites in Australia, Canada, and Europe in participants (aged 18–55 years) with a first unilateral acute optic neuritis episode within 28 days from study baseline. After treatment with high-dose methylprednisolone (1 g/day, intravenously, for 3–5 days), participants were assigned with a computer-generated sequence with permuted block randomisation (1:1) using a centralised interactive voice and web response system to receive 100 mg/kg opicinumab intravenously or placebo once every 4 weeks (six doses) and followed up to week 32. All study participants and all study staff, including the central readers, were masked to treatment assignment apart from the pharmacist responsible for preparing the study treatments and the pharmacy monitor at each site. The primary endpoint was remyelination at 24 weeks, measured as recovery of affected optic nerve conduction latency using full-field visual evoked potential (FF-VEP) versus the unaffected fellow eye at baseline. Analysis was by intention-to-treat (ITT); prespecified per-protocol (PP) analyses were also done. This study is registered with ClinicalTrials.gov, number NCT01721161.

Findings The study was done between Dec 21, 2012, and Oct 21, 2014. 82 participants were enrolled, and 41 in each group comprised the ITT population; 33 participants received opicinumab and 36 received placebo in the PP population. Adjusted mean treatment difference of opicinumab versus placebo was –3·5 ms (17·3 *vs* 20·8 [95% CI –10·6 to 3·7]; 17%; p=0·33) in the ITT population, and –7·6 ms in the PP population (14·7 *vs* 22·2 [–15·1 to 0·0]; 34%; p=0·050) at week 24 and –6·1 ms (15·1 *vs* 21·2 [–12·7 to 0·5]; 29%; p=0·071) in the ITT population and –9·1 ms (13·2 *vs* 22·4 [–16·1 to –2·1]; 41%; p=0·011) in the PP population at week 32. The overall incidence (34 [83%] of 41 in each group) and severity of adverse events (two [5%] of 41 severe adverse events with placebo *vs* three [7%] of 41 with opicinumab) were similar between groups and no significant effects on brain MRI measures were noted in either group (mean T2 lesion volume change, 0·05 mL [SD 0·21] for placebo *vs* 0·20 mL [0·52] with opicinumab; 27 [77%] of 35 participants with no change in gadolinium-enhancing [Gd+] lesion number with opicinumab *vs* 27 [79%] of 34 with placebo; mean 0·4 [SD 0·79 for the placebo group and 0·85 for the opicinumab group] new Gd+ lesions per participant in both groups). Treatment-related serious adverse events were reported in three (7%) of 41 participants in the opicinumab group (hypersensitivity [n=2], asymptomatic increase in transaminase concentrations [n=1]) and none of the participants in the placebo group.

Interpretation Remyelination did not differ significantly between the opicinumab and placebo groups in the ITT population at week 24. However, results from the prespecified PP population suggest that enhancing remyelination in the human CNS with opicinumab might be possible and warrant further clinical investigation.

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Introduction

Leucine-rich repeat and immunoglobulin domain-containing neurite outgrowth inhibitor receptor-interacting protein-1 (LINGO-1) is a negative regulator of oligodendrocyte differentiation and remyelination expressed on oligodendrocytes and neurons of the CNS.[1] LINGO-1 antagonism enhances remyelination in vitro and in animal models of CNS demyelination, including lysolecithin injection into the rat spinal cord, cuprizone demyelination of mouse brain, and rat autoimmune encephalomyelitis.[2–4] LINGO-1 blockade might also afford neuroprotection independently of remyelination as suggested by evidence from rodent models of glaucoma, spinal cord injury, and dopaminergic cell toxicity.[1]

Acute optic neuritis frequently occurs in multiple sclerosis as the first manifestation. Inflammatory demyelination and axonal injury occur, and despite some spontaneous remyelination, most patients are left with residual structural and clinical deficits associated with nerve conduction abnormalities that can be quantified by electrophysiological measures.[5,6] Current treatments for acute optic neuritis are typically high-dose intravenous corticosteroids[7] and plasma exchange.[8] Multiple sclerosis

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed up to March 15, 2016, without language or other restrictions. RENEW was designed as a proof-of-concept study in acute optic neuritis as an in-vivo system to investigate the effect on visual evoked potential (VEP) latency of opicinumab (anti-LINGO-1, BIIB033). To identify previous investigations of remyelination or potential remyelinating agents, we used the terms "optic neuritis" OR "multiple sclerosis" AND "clinical trial" AND "remyelination"; "remyelination" AND "visual evoked potential". These searches identified several articles discussing imaging techniques with potential for assessing remyelinating or neuroreparative therapies, reviews of novel agents for treating multiple sclerosis, trials of intravenous immunoglobulins in multiple sclerosis, pilot studies of insulin-like growth factor-1 in multiple sclerosis, and the remyelinating potential of intravenous immunoglobulins in multiple sclerosis. Several studies in rodents and longitudinal analysis of patients with optic neuritis using VEP were also identified. However, no reports of previous multicentre randomised controlled trials of a potential remyelinating agent were found. We therefore did a further search using the terms "optic neuritis" AND "visual evoked potential" AND "clinical trial" to identify any studies with a similar study population that used VEP as an outcome measure to assess treatment efficacy. This search identified 45 publications, of which three assessed intravenous immunoglobulin, erythropoietin, or simvastatin in participants with optic neuritis using VEP as an outcome. Finally, we searched ClinicalTrials.gov using the terms "optic neuritis" AND "visual evoked potential" to identify potential trials, and PubMed for associated publications using the trial number and name of the responsible party or principal investigator. We identified a study of the potential neuroprotective effects of phenytoin in participants with optic neuritis in which VEP was a secondary endpoint. These reports from single-centre or single-country studies suggested that simvastatin might have an effect on VEP latency, but no treatment effects, as measured by VEP latency, were found with erythropoietin, intravenous immunoglobulin, or phenytoin.

Added value of this study

This is the first multicentre clinical trial investigating the efficacy of opicinumab on VEP latency. Therapies facilitating remyelination, neuroprotection, or neuron repair or regeneration remain an unmet need for CNS demyelinating disorders, and opicinumab was developed as a potential remyelinating agent. Furthermore, novel outcome measures are required to assess remyelination in addition to the clinical outcomes traditionally used. In the RENEW study, participants treated with opicinumab show some improvement in conduction latency recovery versus placebo, but the difference in the intention-to-treat population at 24 weeks was not significant. Our data provide some evidence that supports further clinical investigation of opicinumab as the prespecified per-protocol population and responder analyses showed better recovery with opicinumab than with placebo. The results also confirm the feasibility of including patients with a first acute optic neuritis episode as a target population to test novel CNS remyelinating agents and of using full-field VEP latency as the primary endpoint in international studies.

Implications of all the available evidence

Some findings from our study as well as those of Raftopoulos and colleagues (2016) suggest that it might be possible to prevent neuronal loss and to enhance remyelination following an initial episode of acute optic neuritis. Our results also lend support to the further investigation of the safety and efficacy of opicinumab in patients with multiple sclerosis.

is usually treated with anti-inflammatory disease-modifying therapies to reduce the frequency and severity of future recurrent attacks,[9] but such therapies cannot repair neuronal damage. Therefore, development of therapies facilitating remyelination, neuroprotection, and neuron repair or axonal regeneration remains an important unmet need.[9]

Opicinumab (BIIB033, anti-LINGO-1) is a human monoclonal antibody engineered into an aglycosyl immunoglobulin G subclass 1 framework to reduce effector function.[10] Opicinumab has proven effective in preclinical remyelination and neuroprotection rodent models, independent of inflammation,[1] and good initial tolerability and safety have been shown in phase 1 studies of healthy volunteers and adults with multiple sclerosis.[10]

We assessed for the first time in human beings the safety and tolerability, and the efficacy of opicinumab initiated soon after a first acute optic neuritis episode.

Methods

Study design and participants

This randomised, double-blind, placebo-controlled study (RENEW) was done at 33 sites across Australia, Canada, and Europe.

The study was done in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. All investigators obtained approval from their local ethics committee before study start.

Eligible participants were aged 18–55 years, had a first unilateral onset of acute optic neuritis within 28 days from first symptom onset, and received treatment with 1 g methylprednisolone per day intravenously for 3–5 days before randomisation. The diagnosis of acute optic neuritis required the presence of at least two of the following: reduced visual acuity; afferent pupillary defect; colour vision loss; visual field abnormality; and

pain on eye movement, and was confirmed by study investigators. Visual evoked potential (VEP) alterations were not a diagnostic criterion for acute optic neuritis, but fellow eye VEP latency abnormality was an exclusion criterion (see below). Enrolment was allowed irrespective of whether demyelinating lesions were present on brain MRI, and acute optic neuritis was accepted as the first sign of (newly diagnosed) multiple sclerosis. Exclusion criteria were previous episode of optic neuritis or previous CNS demyelinating event indicative of multiple sclerosis; an established diagnosis of multiple sclerosis (previous to acute optic neuritis onset); refractive errors of –6 dioptres to +6 dioptres or more in either eye; loss of vision not due to acute optic neuritis; an abnormal full-field VEP (FF-VEP) in the fellow eye at screening; and a concomitant ophthalmological disorder (as determined by a physician with expertise in the diagnosis and treatment of ophthalmological disorders, using any assessments felt to be necessary to exclude an alternative diagnosis, and based on their expertise and local standard of care)—eg, diabetic retinopathy, macular degeneration, macular exudate, macular oedema, glaucoma, severe astigmatism, ocular trauma, neuromyelitis optica, ischaemic optic neuropathy, congenital nystagmus, or other ophthalmological conditions that could confound the assessment of functional and anatomical endpoints. Participants with a history or evidence of any of the following were also excluded: severe disc oedema or haemorrhage; any clinically significant cardiac, endocrinological, haematological, hepatic, immunological, metabolic, urological, pulmonary, neurological, dermatological, psychiatric, oncological, renal, severe allergic or anaphylactic reactions, or other major disease; HIV, hepatitis C, or hepatitis B infection; and drug or alcohol abuse in the past 2 years. Participants were excluded if they had been enrolled in another study within the past 3 months or participated in a previous study with opicinumab, were unable to comply with study requirements, or if the investigator felt there were other reasons making participation unsuitable. Women were excluded if pregnant, breastfeeding, or planning to conceive during the study.

All participants provided written informed consent.

Randomisation and masking

Participants were randomly assigned (1:1) to placebo or opicinumab. The allocation sequence was computer generated and randomisation was achieved via a permuted block method using a centralised interactive voice and web response system. The block size was four and the number of blocks was 50. A Biogen biostatistician was responsible for overseeing the randomisation and only the pharmacists preparing treatments or pharmacy monitors were unmasked. Masking was achieved by infusing the same volumes of saline over the same duration regardless of whether the infusion bags contained opicinumab or not. Furthermore, all saline bags were covered with a dark bag before leaving the pharmacy.

Procedures

Participants received opicinumab (100 mg/kg intravenously) or placebo every 4 weeks from baseline to week 20 (six treatments) and assessed up to week 32 (appendix p 3). 100 mg/kg was the highest dose tested in previous phase 1 studies; it was well tolerated, and selected because this study required a concentration greater than EC_{90} (90% effective concentration) as the target efficacious concentration of opicinumab for the human brain is unknown and, under normal conditions, LINGO-1 concentrations in rat CNS (the pharmacology animal model) are lower than in humans.[1] FF-VEP, spectral-domain optical coherence tomography (SD-OCT), and low-contrast letter acuity were assessed at screening, baseline, and every 4–8 weeks to study end (week 32) to assess efficacy.

For FF-VEP measurements, the participant was seated 70–150 cm away from the stimulus (consistent distance at the site level throughout the trial) and then FF-VEP was done with a black and white checkerboard and a 60′ check stimulus size. Stimulus screen luminance and contrast were constant throughout the study. Electrodes were placed according to the Queen Square System and four channels were monitored: left occipital to midfrontal; midoccipital to midfrontal; right occipital to midfrontal; and midfrontal to ear or mastoid. P100 latency was determined from the midoccipital site, where amplitude is maximal.

Because this was the first multicentre study to use VEP latency as a primary endpoint, a rigorous process was followed to ensure reproducibility and consistency. All centres were required to undertake all FF-VEP assessments using a standard protocol developed by the Duke Reading Center (Duke University, Durham, NC, USA) to comply with both the International Society for Clinical Electrophysiology of Vision and the American Clinical Neurophysiology Society guidelines. Detailed instructions on all aspects of VEP training, recording, and submission of data to the central reader for evaluation and assessment of eligibility (on the fellow eye) and for efficacy on the primary endpoint were provided to study site investigators. Before study initiation at the site, each technician had to be certified to do VEP according to the study protocol. For certification, technicians were required to submit VEP studies using the standard protocol on two people, each studied on two separate occasions. The submitted VEP studies were assessed by trained Duke Reading Center VEP readers who ensured that the VEP data were submitted according to study protocol. All data reported were obtained using the Duke Reading Center standard protocol. Site-specific techniques and normative data were used only at the screening visit to determine normalcy of the participants' fellow eye latency, as required by the protocol. Each VEP study was interpreted

independently by two masked clinical electrophysiologists. If the data agreement was not within specified parameters, a third masked independent clinical electrophysiologist arbitrated the data by reconciling the reader disagreements according to his or her best judgment and expertise, and provided the final interpretation. Each VEP measure was interpreted without reference to any of the participant's other VEP data. Central readers were not involved in data collection or analysis.

Study sites were also certified by the Duke Reading Center to obtain SD-OCT scans according to a standardised study protocol. The appendix (p 2) contains details of the protocol, data analysis, and quality control procedures.

Outcomes

The primary endpoint was optic nerve conduction velocity measured by FF-VEP (peak found around 100 ms on the standard VEP in healthy adults [P100]) latency at end of treatment (week 24) in the affected eye, compared with the unaffected eye at baseline. This technique measures electrophysiological responses to patterned visual stimuli:[11] prolongation of VEP latency is associated with inflammatory demyelination in acute optic neuritis, whereas subsequent latency shortening can occur as a result of resolution of inflammation (believed to occur earlier on) and spontaneous remyelination (believed to occur later on).[12] A final latency assessment, as a supportive analysis, was done at study end (week 32).

Secondary endpoints studied another potential opicinumab mechanism of action, the acute neuroprotection of retinal ganglion cells (RGCs) and their axons. Secondary efficacy endpoints assessed at week 24 were change in RGC layer/inner plexiform layer (RGCL/IPL) thickness in the affected eye compared with the unaffected eye at baseline measured by SD-OCT; percentage change in retinal nerve fibre layer (RNFL) thickness in the affected eye versus the unaffected eye at baseline measured by SD-OCT; and change in low-contrast letter acuity of the affected eye from baseline measured using 1·25% and 2·5% Sloan letter charts; the affected eye's own baseline value was used as the baseline covariate.

Additional analyses, based on FF-VEP latency, were number of participants with FF-VEP latency recovery, defined as affected eye FF-VEP latency 10% or less worse than the fellow eye, at week 24 in the per-protocol (PP) and intention-to-treat (ITT) populations (prespecified); also, a post-hoc sensitivity analysis around this recovery threshold was done on the ITT and PP populations to assess whether 10% was an appropriate cutoff. We also assessed mean change in FF-VEP latency at week 24 between treatment groups (ITT population) for participants who received at least four infusions (post-hoc).

All images were assessed centrally for quality control.

Adverse event monitoring was done from administration of first study dose to week 32, and serious adverse event monitoring from screening to week 32. Safety assessments at screening, baseline, and every 4–8 weeks up to week 32 were: physical examination and vital signs; and haematology, blood chemistry, and urinalysis. Participants also had a brain MRI scan (with and without gadolinium [Gd+] enhancement) at screening and week 32; 12-lead electrocardiogram at screening and weeks 24 and 32; assessment of acute optic neuritis signs and symptoms at screening, baseline, and weeks 12, 24, and 32; and measurement of blood drug and anti-opicinumab antibody levels every 4–8 weeks from baseline to week 32 as part of the pharmacokinetic and safety assessments.

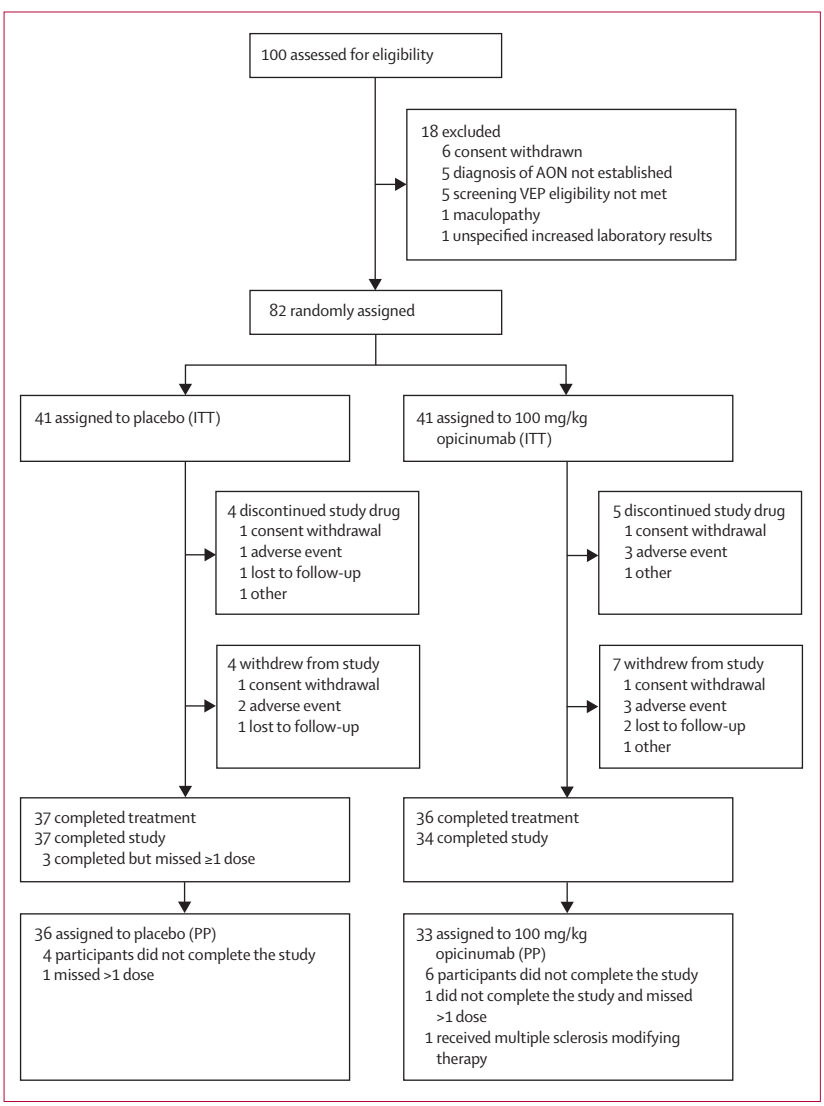

Figure 1: **Trial profile**
ITT=intention-to-treat. AON=acute optic neuritis. PP=per-protocol. VEP=visual evoked potential.

Statistical analysis

The efficacy and safety analyses included all randomised participants who received at least one dose of study

treatment (ITT population). A second prespecified population assessed for efficacy comprised participants who completed the study, missed no more than one study dose, and did not receive multiple sclerosis-specific disease-modifying therapies (prohibited per protocol). These criteria were selected to ensure a population was assessed that had received adequate dosing and a sufficient length of follow-up; this enabled analysis of biological activity without the imputations inherent for early discontinuations in the primary analysis on the ITT population.

When designing the study, the chosen sample size was selected (about 40 participants per treatment group) to have about 80% power to detect a treatment difference between opicinumab and placebo with a one-sided *t* test (α=0·1) if the treatment effect for improvement of VEP latency was at least 50%.

Participant demographics, clinical characteristics, and safety data were summarised with descriptive statistics. For the efficacy endpoints, adjusted mean change (with SE at week 24) was calculated and between-treatment comparisons were evaluated with ANCOVA at week 24 and mixed-effect model repeated measure through week 32. Week 32 data were used as a supportive analysis to check whether treatment effect was sustained between end of treatment (week 24) and end of study (week 32). Last observation carried forward (LOCF) was used to impute missing data at week 24 in the ANCOVA.

The percentage of participants with versus without FF-VEP latency recovery was compared between treatment groups using a χ^2 test; both χ^2 and Fisher's exact tests were used for the sensitivity analyses for the 10% cutoff. Data were analysed with SAS version 9.3.

	Intention-to-treat population			Per-protocol population		
	Placebo (n=41)	Opicinumab (n=41)	All participants (n=82)	Placebo (n=36)	Opicinumab (n=33)	All participants (n=69)
Women	31 (76%)	27 (66%)	58 (71%)	27 (75%)	21 (64%)	48 (70%)
White	39 (95%)	40 (98%)	79 (96%)	35 (97%)	32 (97%)	67 (97%)
Age (years)	32·4 (8·9)	31·8 (7·2)	32·1 (8·0)	32·2 (8·8)	31·2 (7·1)	31·7 (8·0)
Weight (kg)	75·0 (47–119)	71·2 (46–106)	72·2 (46–119)	73·8 (50–119)	72·2 (46–106)	72·5 (46–119)
Height (cm)*	169·0 (155–194)	170·0 (158–188)	170·0 (155–194)	169·5 (155–194)	170·0 (158–188)	170·0 (155–194)
Days from first AON symptom to first dose†	24·6 (3·4)	23·6 (4·0)	24·1 (3·7)	24·3 (3·5)	24·0 (3·8)	24·2 (3·6)
Days from confirmed AON diagnosis to first dose	19·2 (4·9)	18·7 (4·7)	19·0 (4·8)	19·1 (5·0)	19·2 (4·6)	19·1 (4·7)
Participants with affected right eye	19 (46%)	25 (61%)	44 (54%)	16 (44%)	20 (61%)	36 (52%)
Criteria for AON diagnosis						
Decreased visual acuity	36 (88%)	41 (100%)	77 (94%)	31 (86%)	33 (100%)	64 (93%)
Decreased colour vision	30 (73%)	33 (80%)	63 (77%)	27 (75%)	26 (79%)	53 (77%)
Relative afferent pupillary defect	34 (83%)	31 (76%)	65 (79%)	29 (81%)	23 (70%)	52 (75%)
Visual field defect	32 (78%)	37 (90%)	69 (84%)	27 (75%)	30 (91%)	57 (83%)
Ocular pain	31 (76%)	36 (88%)	67 (82%)	27 (75%)	28 (85%)	55 (80%)
Other	5 (12%)	4 (10%)	9 (11%)	5 (14%)	4 (12%)	9 (13%)
AON signs and symptoms at screening or baseline visit‡						
Visual field defect	29 (71%)	34 (83%)	63 (77%)	25 (69%)	27 (82%)	52 (75%)
Colour desaturation	33 (80%)	32 (78%)	65 (79%)	28 (78%)	25 (76%)	53 (77%)
Uhthoff's symptom	8 (20%)	18 (44%)	26 (32%)	6 (17%)	16 (48%)	22 (32%)
Swollen optic disc	8 (20%)	12 (29%)	20 (24%)	6 (17%)	11 (33%)	17 (25%)
Relative afferent pupillary defect	33 (80%)	30 (73%)	63 (77%)	28 (78%)	24 (73%)	52 (75%)
FF-VEP conduction block in the affected eye at baseline	5 (12%)	10 (24%)	15 (18%)	5 (14%)	6 (18%)	11 (16%)
FF-VEP latency in the fellow eye at baseline (ms)	101·7 (5·3)	102·7 (6·4)	102·2 (5·8)	101·0 (4·9)	102·6 (6·1)	101·8 (5·5)
RGCL/IPL thickness in the affected eye at baseline (µm)§	66·0 (6·9)	63·8 (7·4)	64·8 (7·2)	65·9 (7·2)	63·6 (8·1)	64·8 (7·7)
Number of participants with Gd+ lesions before first dose¶	7 (18%)	2 (5%)	9 (12%)	5 (15%)	1 (3%)	6 (9%)
Number of brain Gd+ lesions before first dose¶	0·5 (1·6)	0·2 (1·0)	0·4 (1·4)	0·2 (0·7)	0·1 (0·4)	0·1 (0·5)
Number of participants with T2 lesions before first dose¶	32 (84%)	29 (76%)	61 (80%)	29 (85%)	25 (76%)	54 (81%)
Volume of brain T2 lesions before first dose (mL)¶	1·09 (1·32)	1·09 (1·90)	1·09 (1·63)	0·95 (1·03)	0·84 (1·55)	0·89 (1·30)

AON=acute optic neuritis. FF-VEP=full-field visual evoked potentials. Gd+=gadolinium-enhancing. RGCL/IPL=retinal ganglion cell layer/inner plexiform retinal layer. ITT=intention-to-treat. PP=per-protocol. *n=39 in each group; total n=78 for the ITT population; n=34 in the placebo group; n=31 in the opicinumab group; total n=65 in the PP population. †First dose given, on average, 2 weeks after completion of high-dose intravenous methylprednisolone treatment (1 g daily for 3–5 days). ‡Symptoms were not uniformly tested in accordance with a predefined protocol. §n=38 in the placebo group and n=40 in the opicinumab group, total=78 for the ITT population; n=34 in the placebo group and n=32 in the opicinumab group, total=66 for the PP population. ¶n=38 in each group, total=76 for the ITT population; n=34 in the placebo group and n=33 in the opicinumab group, total=67 for the PP population.

***Table 1*: Demographic and clinical characteristics of participants**

An internal safety monitoring committee (comprising manuscript coauthors [DC, SF, and LX]) oversaw the study.

Due to reading differences between Cirrus (Carl Zeiss Meditec, Dublin, CA, USA) and Spectralis (Heidelberg Engineering, Heidelberg, Germany) manufacturing analysis software, RNFL thinning was reported as a percentage. By contrast, a value in µm was used for RGCL/IPL thinning because the reading centre analysis software gives identical results with both Cirrus and Spectralis scans.

This study is registered with ClinicalTrials.gov, number NCT01721161.

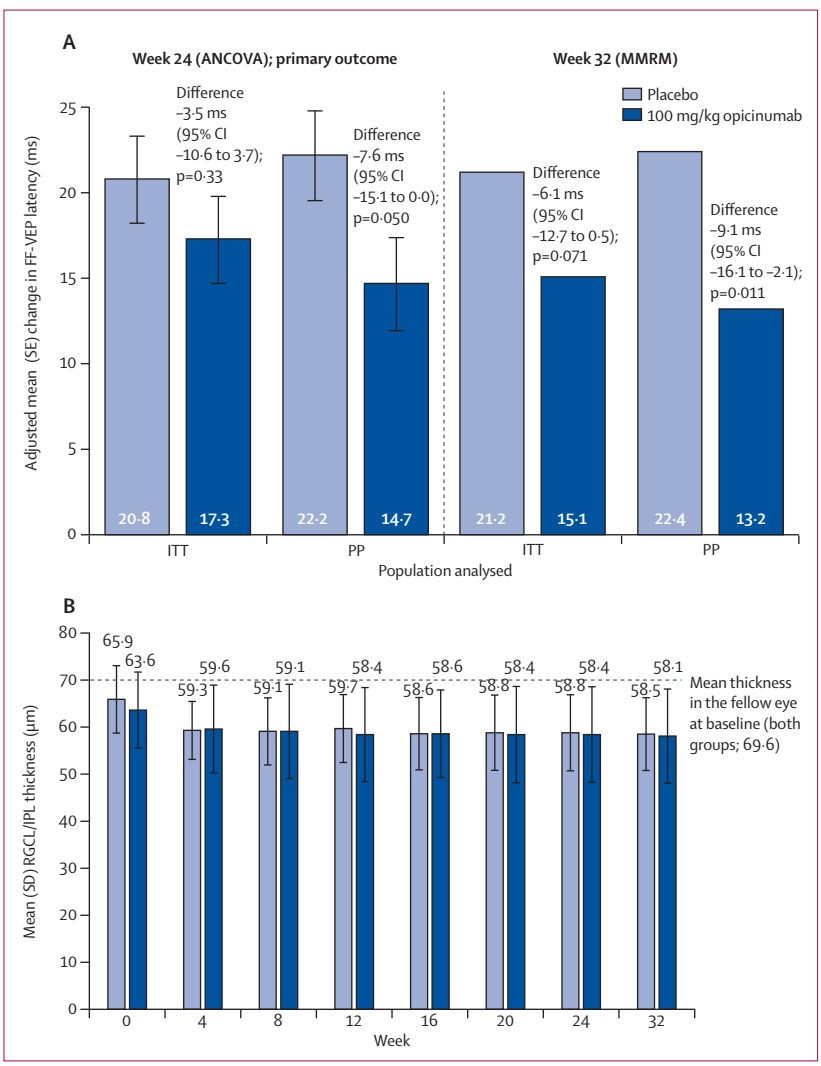

Figure 2: **Change in VEP latency (A) and OCT thickness (B) outcomes**
Adjusted mean change in optic nerve conduction latency was measured by FF-VEP in the affected eye compared with the unaffected fellow eye at baseline in the PP and ITT populations at week 24 (by ANCOVA) and week 32 (by MMRM). Mean (SD) RGCL/IPL thickness at each visit was measured by spectral-domain optical coherence tomography in the affected eye in the PP population up to week 32. PP=placebo, n=36; opicinumab, n=33. ITT: n=41, both groups. FF-VEP=full-field visual evoked potential. ITT=intention-to-treat. MMRM=mixed-effect model repeated measure. PP=per-protocol. RGCL/IPL=retinal ganglion cell layer/inner plexiform layer. SEs were not calculated for week 32 data.

Role of the funding source
The funder of the study was involved in the study design, conduct, data analysis, and data interpretation, drafting and review of the report, and the decision to submit for publication, all in collaboration with the coauthors. The corresponding author had full access to all data from the study (along with the coauthors) and had final responsibility for the decision to submit the manuscript.

Results

The study was done between Dec 21, 2012, and Oct 21, 2014. 100 participants were screened and of these 82 participants were randomly assigned to placebo or opicinumab at 33 sites across Australia, Canada, and Europe. Median number of participants per site was two (mode one, range 1–7). The ITT population comprised 41 participants in each treatment group, whereas in the PP population 33 received opicinumab and 36 placebo (figure 1). The groups had similar baseline demographics (table 1), participants withdrawing from the study, and treatment discontinuation (figure 1). However, severe cases of acute optic neuritis were randomised more frequently to the opicinumab group than to the placebo group as shown by the prevalence of conduction block (2:1, respectively) and presence of several acute optic neuritis signs and symptoms at screening or baseline (table 1).

Improvement in optic nerve conduction velocity (primary endpoint) was indicated by shorter latency. The results showed some shortening of latency with opicinumab versus placebo in the ITT population at week 24 (adjusted mean of treatment difference: –3·5 ms [17·3 (SE 2·5) *vs* 20·8 (2·5); 95% CI –10·6 to 3·7; p=0·33], 17% improvement) and week 32 (–6·1 ms [15·1 *vs* 21·2; 95% CI –12·7 to 0·5; p=0·071], 29% improvement). The difference was significant in the PP population at week 32 (–9·1 ms [13·2 *vs* 22·4; 95% CI –16·1 to –2·1; p=0·011], 41% improvement; figure 2A) but not at week 24 (–7·6 ms [14·7 (SE 2·7) *vs* 22·2 (2·6); 95% CI –15·1 to 0·0; p=0·050], 34% improvement).

No treatment effect was noted for the secondary efficacy endpoints of RNFL and RGCL/IPL thickness by SD-OCT or change in low-contrast letter acuity for placebo versus opicinumab at week 24 (table 2). However, most RGCL/IPL thinning occurred before the first administration of the study dose and all RGCL/IPL thinning had occurred before the second dose was given in week 4 (table 1, figure 2B, appendix p 5; corresponding fellow eye data are given on appendix p 6).

The numbers and proportions of participants with an adverse event and severity of adverse events were similar between placebo and opicinumab, with 34 participants in each group (83%) having at least one adverse event (table 3). Five adverse events occurred in 10% or more of participants: fatigue, nausea, headache, nasopharyngitis, and Uhthoff's phenomenon (table 3).

The number of participants with a serious adverse event or discontinuing treatment was higher in the

	Intention-to-treat analyses		Per-protocol analyses	
	Placebo (n=41)	Opicinumab (n=41)	Placebo (n=36)	Opicinumab (n=33)
Mean percentage change (SE) in RNFL thickness (SD-OCT)*; affected eye at week 24 *vs* baseline fellow eye	−11·8 (2·1)	−15·7 (2·0)	−12·2 (2·3)	−17·0 (2·3)
Treatment difference at week 24 *vs* placebo (95% CI)*	−3·9 (−9·7 to 1·9)	..	−4·8 (−11·3 to 1·7)	..
p value	0·19	..	0·15	..
Mean change (SE) in RGCL/IPL thickness (μm)*; affected eye at week 24 *vs* baseline fellow eye	−9·9 (1·2)	−11·1 (1·2)	−10·2 (1·3)	−11·9 (1·4)
Treatment difference at week 24 *vs* placebo (95% CI)*	−1·2 (−4·5 to 2·2)	..	−1·8 (−5·5 to 2·0)	..
p value	0·50	..	0·35	..
Mean change (SE) in LCLA (1·25% Sloan chart)†; affected eye at week 24 *vs* baseline	8·1 (1·8)	6·5 (1·9)	7·2 (1·8)	6·0 (2·0)
Treatment difference at week 24 *vs* placebo (95% CI)†	−1·6 (−6·9 to 3·6)	..	−1·2 (−6·6 to 4·3)	..
p value	0·54	..	0·66	..
Mean change (SE) in LCLA (2·5% Sloan chart)†; affected eye at week 24 *vs* baseline	11·9 (2·0)	11·0 (2·0)	11·6 (2·0)	10·8 (2·2)
Treatment difference at week 24 *vs* placebo (95% CI)†	−0·8 (−6·5 to 4·9)	..	−0·8 (−6·7 to 5·2)	..
p value	0·77	..	0·80	..

RNFL=retinal nerve fibre layer. RGCL/IPL=retinal ganglion cell layer/inner plexiform retinal layer. SD-OCT=spectral-domain optical coherence tomography. LCLA=low-contrast letter acuity. *A decrease (negative value) represents loss of RNFL thickness; the difference versus placebo represents the more severe acute optic neuritis evident pretreatment initiation in the opicinumab group (table 1). †An increase in LCLA from baseline represents recovery; a negative difference versus placebo indicates no treatment effect.

***Table 2*: Secondary efficacy outcomes at week 24**

opicinumab group (table 3). Of the two participants (5%) in the placebo group who had a serious adverse event, one had viral pericarditis and tested positive for cytomegalovirus and one developed multiple sclerosis. Of the five participants (12%) in the opicinumab group who had serious adverse events, one participant had a multiple sclerosis relapse and one had optic neuritis in the fellow eye; two cases of hypersensitivity reactions that occurred shortly after the start of the second infusion and one asymptomatic case of increased alanine and aspartate aminotransferases (reported as hepatopathy and first observed after the second infusion) were considered treatment related. The three participants with treatment-related serious adverse events in the opicinumab group discontinued treatment in addition to the placebo-treated participant who developed multiple sclerosis (table 3). All serious adverse events reported as treatment related resolved on treatment discontinuation.

The incidence of adverse events by System Organ Class (SOC) was generally similar between groups and the SOCs with the most frequent events (≥10% of total participants) are presented in table 3. Events in the gastrointestinal SOC occurred more frequently (≥10% difference) in participants in the opicinumab group (12 [29%]) than in the placebo group (five [12%]). The most commonly reported gastrointestinal symptoms were nausea (five [12%] in the opicinumab group *vs* three [7%] in the placebo group) and dyspepsia (two [5%] *vs* one [2%]).

The number of participants with an adverse event occurring within 4 h after the start of an infusion was higher in participants in the opicinumab group than in those in the placebo group (appendix p 7). The same event did not occur with every infusion (data not shown). Adverse events were most frequent after the second and third infusions, and the most common infusion-related adverse events in the opicinumab group were headache (three [7%]) and nausea (three [7%]), and in the placebo group was dysgeusia (one [2%]).

17 participants had weight gain of more than 7% from baseline: four from the placebo group (10%) and 13 from the opicinumab group (32%). Three participants had weight decrease of more than 7% (two in the placebo group *vs* one in the opicinumab group). Mean change in weight and percentage change from baseline at week 24 in the placebo group were 0·69 kg (SD 2·15) and 0·81% (2·88), and in the opicinumab group were 2·88 kg (3·56) and 3·86% (4·85). No participants died in either the opicinumab or placebo group.

Other safety and tolerability investigations were similar between groups and no immunogenicity was noted. No evidence of worsening of T2 lesion volume was shown (mean 0·05 mL [SD 0·21]; median 0·017 [IQR 0·000–0·146] in the placebo group *vs* 0·20 mL [0·52]; median 0·003 [IQR 0·000–0·232] in the opicinumab group), or change in Gd+ lesion number (0·14 [0·73; 27 (77%) of 35 participants had no change] in the placebo group *vs* 0·32 [0·81; 27 (79%) of 34] in the opicinumab group) from screening to week 32 (appendix p 8). Additionally, minimal enhancing activity was noted in both groups at week 32 (mean 0·4 new Gd+ lesions per participant in both groups [0·4 (SD 0·79) in the placebo group *vs* 0·4 (0·85) in the opicinumab group]).

In a post-hoc analysis of participants from the ITT population who received at least four infusions, improvement in FF-VEP latency at week 24 was similar to the primary endpoint analysis for the PP population

	Placebo (n=41)	Opicinumab (n=41)	All participants (n=82)
Summary of adverse events			
Any adverse event	34 (83%)	34 (83%)	68 (83%)
Serious adverse event	2 (5%)	5 (12%)	7 (9%)
Treatment-related serious adverse event	0	3 (7%)	3 (4%)
Discontinued treatment due to adverse event	1 (2%)	3 (7%)	4 (5%)
Withdrew from study due to adverse event	2 (5%)	3 (7%)	5 (6%)
Severity of events			
Mild	12 (29%)	13 (32%)	25 (30%)
Moderate	20 (49%)	18 (44%)	38 (46%)
Severe	2 (5%)	3 (7%)	5 (6%)
Adverse events occurring in ≥10% of total participants			
Nasopharyngitis	13 (32%)	12 (29%)	25 (30%)
Headache	11 (27%)	11 (27%)	22 (27%)
Fatigue	5 (12%)	6 (15%)	11 (13%)
Uhthoff's phenomenon	6 (15%)	3 (7%)	9 (11%)
Nausea	3 (7%)	5 (12%)	8 (10%)
Incidence by SOC for adverse events occurring in ≥10% of total participants*			
Nervous system disorders	22 (54%)	22 (54%)	44 (54%)
Infections and infestations	22 (54%)	19 (46%)	41 (50%)
General disorders and administration site conditions	10 (24%)	9 (22%)	19 (23%)
Gastrointestinal disorders	5 (12%)	12 (29%)	17 (21%)
Eye disorders (other than the initial report of AON)	7 (17%)	8 (20%)	15 (18%)
Musculoskeletal and connective tissue disorders	7 (17%)	8 (20%)	15 (18%)
Skin and subcutaneous tissue disorders	7 (17%)	6 (15%)	13 (16%)
Investigations (abnormal clinical or laboratory test)	3 (7%)	6 (15%)	9 (11%)
Respiratory, thoracic, and mediastinal disorders	4 (10%)	4 (10%)	8 (10%)

SOC=System Organ Class. AON=acute optic neuritis. *A participant was counted only once within each SOC and preferred adverse event term.

***Table 3*: Adverse events**

analysis: adjusted mean change of 22·0 ms (placebo; n=38) versus 15·8 ms (opicinumab; n=37), a treatment difference versus placebo of –6·1 ms (95% CI –13·3 to 1·1; 28% improvement; p=0·096) using ANCOVA analysis. Whether the reduced efficacy in the ITT population was due to the LOCF imputation or insufficient treatment was unclear. However, results from this post-hoc analysis show that insufficient treatment (ie, fewer than four treatments from baseline to 20 weeks) was the major contributor.

Among participants in the ITT population whose FF-VEP latency was impaired in the affected eye at baseline (defined as >3% worse than fellow eye or with conduction block), the number of participants with normal or mildly prolonged FF-VEP latency (defined as ≤10% worse than fellow eye) at week 24 was 16 (53%) of 30 in the opicinumab group and nine (26%) of 34 in the placebo group (p=0·028). At week 12, ten (29%) of 35 participants in the opicinumab group and four (12%) of 33 participants in the placebo group had normal or mildly prolonged FF-VEP latency (p=0·094). Similar results were noted in the PP population with 15 (54%) of 28 participants in the opicinumab group and nine (27%) of 33 participants in the placebo groups having normal or mildly prolonged FF-VEP latency at week 24 (p=0·036) and nine (30%) of 30 participants in the opicinumab group and four (13%) of 31 participants in the placebo group at week 12 (p=0·10). Post-hoc sensitivity analyses done in the PP population showed that 10% was an appropriate cutoff to indicate latency recovery (appendix p 9).

FF-VEP latency in the affected eye did not change over the course of the study, as shown in the appendix (p 10).

Discussion

Results of this study did not show a significant difference in the change in FF-VEP latency at week 24 (primary endpoint) between the opicinumab and placebo groups in the ITT population. However, significant differences were observed in the PP population at week 32.

RENEW is the first multicentre randomised clinical trial investigating the efficacy of opicinumab and selected recovery of FF-VEP latency in the affected eye as the primary efficacy outcome. VEP latency is a sensitive measure of demyelination and subsequent remyelination in optic neuritis models.[13–15] In participants presenting with an episode of acute optic neuritis, such as those enrolled in RENEW, baseline affected eye latency from demyelination cannot be assessed because of oedema and the frequent prevalence of conduction block. To overcome this limitation in the design of the RENEW study, we calculated the difference in affected eye VEP latency over time using the unaffected fellow eye baseline value as the pretreatment normal reference value.[12,16] Although variable between individuals,[11] VEP usually has a very small inter-eye latency variation in the absence of disease pathology and is highly reproducible for sequential testing under standardised testing conditions.[12,16,17] To ensure that the baseline of the fellow eye was normal, participants with a diagnosis of multiple sclerosis or ophthalmological disorders were excluded and the fellow eye had to have a normal VEP at screening.

In acute optic neuritis, inflammation and optic nerve demyelination result in prolonged VEP latency; following acute optic neuritis, a number of processes, including inflammation resolution earlier on and remyelination later on, result in incomplete VEP latency recovery over 6 months.[12,18,19] VEP has been used in animal models to assess neurological or potential effects on remyelination of the adenosine A1 receptor agonist N6-cyclohexyl-adenosine and siRNAs against the Nogo receptor.[20,21] VEP was also used in single or small multicentre clinical studies assessing high-dose intravenous immunoglobulin, erythropoietin, simvastatin, and phenytoin in patients with acute optic neuritis,[22–25] and in natural recovery observational studies after an acute optic neuritis episode.[12,16,17,26–28]

When baseline characteristics of participants enrolled in RENEW were compared with those in trials of other candidate remyelinating or neuroprotective drugs, age and percentage of women were similar,[7,22–25] whereas

mean number of days from first acute optic neuritis symptom to first dose was 24 days in RENEW versus 5–20 days in previous acute optic neuritis studies.[7,22–25] A study testing erythropoietin reported shorter VEP latencies at week 16 for erythropoietin than for placebo, but the reported VEP latency was already shorter at baseline, resulting in an absence of treatment effect.[23] A significant effect on VEP latency was reported for simvastatin using imputation for not detectable baseline affected eye values, but not for intravenous immunoglobulin or phenytoin.[22,24,25] When comparing these trials it should be noted that RENEW is a multicentre trial and was designed to overcome the limitation of not detectable baseline affected eye FF-VEP latency, by using the fellow healthy eye, and to use FF-VEP latency to determine change from baseline, with rigorous procedures for performance, central reading, and standardisation of latency measurement.

Outcome measures of remyelination were selected as the primary endpoints because the available preclinical data indicated a mechanism of action on this effect.[2–4] Because the efficacy of remyelination depends on axonal survival, we thought it was important to also investigate neuroprotective activity, even though efficacy on neuroprotection was hard to prove since it probably depends on very early administration of therapy.[5] Therefore, the study's secondary endpoints investigated potential neuroprotection after acute inflammatory injury to the RGC neurons as a result of acute optic neuritis, using SD-OCT and low-contrast letter acuity measures, and no effect of opicinumab was observed. However, the results showed that most retinal thinning occurred well before treatment started and all before the second dose (week 4). In view of the early occurrence of damage in acute optic neuritis, these data confirm and highlight the need to intervene even sooner than we did in RENEW in future trials testing the neuroprotection of RGCs, and suggest treatment should begin within days rather than weeks after acute optic neuritis onset.[25] This limited therapeutic intervention window for RGC protection was not seen for optic nerve remyelination, as evidenced from the observed VEP latency data with opicinumab. Hence, longer therapeutic intervention windows for remyelination should be explored with this and future candidate remyelinating agents. Notably, the clinical endpoints affected by the primary (VEP latency) and secondary (OCT) endpoints are currently not well understood. However, some data indicate that detection of motion tests correlate with VEP latency recovery and low-contrast letter acuity correlates with preservation of OCT endpoints.[29,30]

Acute optic neuritis without other brain lesions is known to have a lower risk of conversion to clinically definite multiple sclerosis than does acute optic neuritis with brain lesions,[31] but little is known about differences or similarities in the severity of demyelination and extent of spontaneous remyelination in these two clinical scenarios. In RENEW, participants with and without other cerebral lesions were enrolled. Investigation of opicinumab as a remyelinating treatment for patients with multiple sclerosis and pre-existing lesions of longer duration was undertaken in the SYNERGY study (NCT01864148). This now completed trial investigated 3 mg/kg, 10 mg/kg, 30 mg/kg, or 100 mg/kg opicinumab given intravenously compared with placebo (19 doses) over 84 weeks in participants concurrently treated with 30 µg intramuscular interferon beta-1a.

The safety analyses confirmed that the overall incidence and severity of adverse events with opicinumab was similar to placebo. Three participants had serious adverse events reported as treatment related: two hypersensitivity reactions occurring shortly after the start of the second study drug infusion and one with an asymptomatic elevation in transaminases reported as hepatopathy. All three events resolved after treatment discontinuation. Weight gain greater than 7% was more frequent with opicinumab than with placebo and participants who had weight gain with opicinumab had worse baseline acute optic neuritis disease characteristics (data not shown). No evidence of weight gain was observed in previous clinical studies of opicinumab,[10] but this adverse event merits further investigation in future studies. Overall, assessment of the safety of opicinumab is restricted by the relatively small and highly selected cohort and limited duration of exposure (32 weeks).

Although the dose used in RENEW is high for a monoclonal antibody (100 mg/kg compared with 150 mg for daclizumab and 300 mg for natalizumab[32,33]), it is much lower than the intravenous immunoglobulin dose used in the trial assessing remyelination following acute optic neuritis (400 mg/kg).[22] For example, 100 mg/kg opicinumab provides a maximum mean concentration of 2·7 mg/mL (SD 0·7) immunoglobulin G,[10] which is within the variability of normal total immunoglobulin G concentrations in adults (11·6 mg/mL [3·1][34]). Notably, unlike intravenous immunoglobulin, opicinumab was specifically engineered to reduce effector function and complement activation (unpublished) so intravenous immunoglobulin-like effects are unlikely to explain the observed results.

Statistical significance for FF-VEP latency was only reached in the PP population at week 32 (p=0·01). This might be explained by the sample size and hence power of this study being small and there was uncertainty at the time of the study design on the duration of therapeutic remyelination following acute optic neuritis. The sample size was simply an estimate because at study design the actual magnitude of the treatment effect of opicinumab was unknown. Also, the required treatment duration for optimal therapeutic remyelination, adequate balancing of baseline characteristics by randomisation, early terminations, and other actual events occurring in phase 2a trials with novel drugs such as opicinumab, are difficult to predict, and all affect the actual power of the

study. These events include participants who withdrew from the study early because of adverse events at a time when latency delay can be severe, loss to follow-up, and withdrawal of consent, and applied to four (10%) participants in the placebo group and seven (17%) participants in the opicinumab group. Importantly, for imputation of missing data, in the ITT primary analysis the FF-VEP latency value at the last available visit was carried forward in the primary ANCOVA analysis at week 24. Based on the observed treatment effects, the actual power in this study was 16% for the ITT population and 58% for the PP population. Furthermore, the prespecified analysis of efficacy on the primary endpoint at the individual level showed that the affected eye FF-VEP latency recovered to normal or near normal in twice as many participants treated with opicinumab than with placebo in both the ITT and PP populations, whereas the observed recovery rate with placebo was consistent with predictions from previous natural history studies with FF-VEP at less than 30%.[17,19]

Furthermore, the therapeutic intervention window to prevent retinal thinning was found to be small and very early in the disease course. These factors all restricted the ability to test the hypothesis of neuroprotection of RGCs with opicinumab following acute optic neuritis.

A major challenge in drug development is the translation of preclinical pharmacological observations into efficacy in human clinical trials. The findings from the RENEW study suggest that enhancement of remyelination in the human CNS with opicinumab might be possible and provide valuable information about the design of subsequent studies. The results confirm the feasibility of using participants with a first acute optic neuritis episode as a target population to test novel CNS remyelinating and neuroprotective agents (also supported by the recent phenytoin study[25]), and FF-VEP latency as the primary biomarker endpoint in global studies of remyelinating therapies.[5] Future trials with earlier administration of opicinumab following acute injury and with other CNS demyelinating lesions such as multiple sclerosis are needed to confirm its use as a CNS remyelinating and neuroprotective drug candidate.

Contributors

DC, LB, SG, YC, LX, and SF designed the study with input from the other authors and were responsible for the conduct and data analysis of the study. GJJ and MS were responsible for the VEP and SD-OCT protocols, methodology, and infrastructure, and were involved in design of the study. OA, TZ, LV, JF, HB, FZ, and LM collected study data and gave input on analysis. MS reviewed all of the VEP data submitted to the central reading centre. YC and LX analysed the data and all authors were involved in data interpretation.

Declaration of interests

DC reports he was a full-time paid employee of Biogen, owns stock in Biogen, and has been named as one of the inventors on patents pending relating to treatment of acute optic neuritis and multiple sclerosis with anti-LINGO-1. LB reports consulting fees from Biogen during the conduct of the study. SG reports personal fees from Biogen during the conduct of the study. OA reports grants from the German Research Foundation (DFG) and the German Ministry of Education and Research; grants and personal fees from Bayer HealthCare, Biogen, Novartis, and Teva; and personal fees from Genzyme, MedImmune, and Merck Serono outside of the submitted work. TZ reports grants and personal fees from Biogen outside of the submitted work; consulting fees from Almirall, Bayer HealthCare, Biogen, Genzyme, GlaxoSmithKline, Merck Serono, MSD, Novartis, Sanofi-Aventis, Synthon, and Teva; and research support from Bayer HealthCare, Biogen, Merck Serono, Novartis, Sanofi-Aventis, and Teva. LV reports personal fees and non-financial support from Biogen, Genzyme, Merck Serono, and Novartis outside of the submitted work. JF reports personal fees from Almirall, Biogen, Genzyme, Merck Serono, Novartis, Sanofi-Aventis, and Teva for participation in scientific boards; speaker honoraria from Biogen, Merck Serono, and Teva; and personal fees for advising on preclinical development from Takeda outside of the submitted work. MS reports grants from Biogen during the conduct of the study and personal fees from Biogen, grants and personal fees from Novartis, personal fees from EMD/Serono, other support from Osmotica (data safety monitoring board), and consulting fees from Genentech and Genzyme outside of the submitted work. GJJ reports personal fees from Heidelberg Engineering outside of the submitted work. HB reports personal fees from Biogen, Genzyme, Oxford PharmaGenesis, Novartis, and Roche, and grants from Biogen and Novartis outside of the submitted work. FZ reports consulting fees from Alimera, Allergan, Bayer HealthCare, and Novartis and grants from Novartis outside of the submitted work. LM reports grants from Biogen during the conduct of the study and non-financial support from Biogen, Genzyme, Merck Serono, Novartis, and Teva outside of the submitted work. YC reports he is an employee of and stockholder in Biogen. LX reports he is an employee of and stockholder in Biogen. SF reports she was an employee of and stockholder in Biogen.

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