Safety and efficacy of opicinumab in patients with relapsing multiple sclerosis (SYNERGY): a randomised, placebo-controlled, phase 2 trial

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Summary

Background Opicinumab is a human monoclonal antibody against LINGO-1, an inhibitor of oligodendrocyte differentiation and axonal regeneration. Previous findings suggested that opicinumab treatment might enhance remyelination in patients with CNS demyelinating diseases. We aimed to assess the safety and efficacy of opicinumab in patients with relapsing multiple sclerosis.

Methods We did a randomised, double-blind, placebo-controlled, dose-ranging, phase 2 study (SYNERGY) at 72 sites in 12 countries. Participants (aged 18–58 years) with relapsing multiple sclerosis (relapsing-remitting multiple sclerosis and secondary progressive multiple sclerosis with relapses) were randomised in a 1:2:2:2:2 ratio by an interactive voice and web response system to opicinumab 3 mg/kg, 10 mg/kg, 30 mg/kg, or 100 mg/kg, or placebo. An identical volume of study drug was administered intravenously once every 4 weeks. All participants self-administered intramuscular interferon beta-1a as background anti-inflammatory treatment once a week. The primary endpoint was the percentage of participants achieving confirmed disability improvement over 72 weeks, which was a multicomponent endpoint measured by the Expanded Disability Status Scale, the Timed 25-Foot Walk, the Nine-Hole Peg Test, and the 3 s Paced Auditory Serial Addition Test. The primary endpoint was analysed under intention-to-treat principles. This study is registered at ClinicalTrials.gov, number NCT01864148.

Findings Between Aug 13, 2013, and July 31, 2014, 419 patients were enrolled and randomly assigned either placebo (n=93) or opicinumab 3 mg/kg (n=45), 10 mg/kg (n=95), 30 mg/kg (n=94; one patient did not receive the assigned treatment), or 100 mg/kg (n=92). The last patient visit was on March 29, 2016. Confirmed disability improvement over 72 weeks was seen in 45 (49%) of 91 patients assigned to placebo, 21 (47%) of 45 assigned to opicinumab 3 mg/kg, 59 (63%) of 94 assigned to opicinumab 10 mg/kg, 59 (65%) of 91 assigned to opicinumab 30 mg/kg, and 36 (40%) of 91 assigned to opicinumab 100 mg/kg. A linear dose-response in the probability of confirmed disability improvement was not seen (linear trend test p=0·89). Adverse events occurred in 79 (85%) patients assigned placebo and in 275 (85%) assigned any dose of opicinumab. The most common adverse events of any grade in patients assigned any dose of opicinumab included influenza-like illness (140 [43%] with any dose of opicinumab *vs* 37 [40%] with placebo), multiple sclerosis relapses (117 [36%] *vs* 30 [32%]), and headache (51 [16%] *vs* 23 [25%]). Serious adverse events reported as related to treatment were urinary tract infection in one (1%) participant in the the placebo group, suicidal ideation and intentional overdose in one (1%) participant in the 30 mg/kg opicinumab group, bipolar disorder in one (1%) participant in the 100 mg/kg opicinumab group, and hypersensitivity in four (4%) participants in the 100 mg/kg opicinumab group. One patient in the opicinumab 30 mg/kg group died during the study due to a traffic accident, which was not considered related to study treatment.

Interpretation Our findings did not show a significant dose-linear improvement in disability compared with placebo in patients with relapsing multiple sclerosis. Further studies are needed to investigate whether some subpopulations identified in the study might benefit from opicinumab treatment at an optimum dose.

Funding Biogen.

Introduction

Multiple sclerosis is a disabling disease characterised by chronic CNS inflammation, demyelination, and axonal loss.[1] More than a dozen anti-inflammatory disease-modifying treatments are now available that might reduce the frequency of relapses and delay the worsening of disability.[2] However, neuroreparative treatments that reverse pre-existing disability and improve neurological function are an important unmet need.[3]

LINGO-1 is a cell-surface glycoprotein selectively expressed on CNS neurons and oligodendrocytes.[4] This protein inhibits oligodendrocyte differentiation, myelination,

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for reports published in English before Jan 26, 2018, with the terms: ("remyelinating" OR "remyelin*" OR "remyelination" OR "myelin repair") AND ("multiple sclerosis" OR "acute optic neuritis"), and with the filter "clinical trial". Opicinumab is a fully human IgG1 monoclonal antibody against LINGO-1, which inhibits oligodendrocyte differentiation, myelination, and axonal growth. The multicentre, randomised, phase 2 RENEW study was a proof-of-concept study that assessed opicinumab in patients with a first episode of acute optic neuritis. The primary analysis did not show significant results, but participants treated with opicinumab showed numerical improvements in conduction latency recovery when compared with participants given a placebo, suggesting that enhancement of remyelination in the human CNS with opicinumab might be possible. We identified four other randomised controlled trials that assessed the effects of drug candidates postulated to have remyelination effects in patients with CNS demyelinating disease. While results from these early trials suggest modest improvement in some biomarkers related to remyelination, none of these study drugs has been proven to reverse neurological disability due to remyelination in multiple sclerosis.

Added value of this study

SYNERGY is the first double-blind randomised study to assess the efficacy and safety of opicinumab in participants with relapsing multiple sclerosis. Findings from this multinational dose-ranging study did not show significant linear dose-related confirmed improvements in disability. However, the findings generated hypotheses that could inform the design of future remyelination trials using imaging biomarkers to identify patient populations and to select potentially more sensitive clinical endpoints. For example, the SYNERGY study provided data for two novel predefined efficacy endpoints: a multicomponent clinical primary endpoint to capture more fully the effect of treatment on the major dimensions of neurological disability associated with multiple sclerosis; and the endpoint of overall response score, to allow integrated assessment of disability improvement and worsening over time.

Implications of all the available evidence

Preliminary evidence suggests that enhancement of oligodendrocyte differentiation might facilitate remyelination that could potentially reverse neurological disability in patients with multiple sclerosis. Future studies will need to address the challenges of identifying the population that might respond to remyelination treatments, and the development of more sensitive and specific outcome measures for remyelination. The phase 2 AFFINITY study (NCT03222973) of opicinumab as an add-on to multiple anti-inflammatory disease-modifying treatments has been initiated to assess the efficacy and safety of opicinumab in a targeted population of patients with relapsing multiple sclerosis identified from SYNERGY.

neuronal survival, and axonal regeneration.[5–8] Expression of LINGO-1 is upregulated in diverse CNS neuropathologies, including in multiple sclerosis lesions.[8,9]

Opicinumab is a fully human IgG1 aglycosylated monoclonal antibody against LINGO-1 with greatly reduced Fcγ and complement effector functions.[8] LINGO-1 blockade with antibodies against LINGO-1 (anti-LINGO-1) facilitates axonal myelination in vitro[6,7] and remyelination in several in vivo demyelination models[7] through enhanced differentiation of oligodendrocyte precursor cells. Moreover, experimental autoimmune encephalomyelitis in LINGO-1 knockout mice versus wild-type mice was clinically milder and correlated histologically with increased spinal cord remyelination.[6,10] There is no evidence that opicinumab has any immunomodulatory effects, as assessed by T-cell proliferation and cytokine production in vitro, and by gene expression analysis in blood and CSF cells from opicinumab-treated patients with multiple sclerosis.[11] The randomised, placebo-controlled, phase 2 RENEW study[12,13] in patients with their first episode of acute optic neuritis suggested a possible clinical effect of opicinumab by showing improved recovery in optic nerve conduction measured by visual evoked potential (although findings were not significant).

Here, we report the results of the SYNERGY study, which was designed to investigate the clinical safety, efficacy, and pharmacokinetics of four different doses of opicinumab versus placebo added on to intramuscular interferon beta-1a over 72 weeks in patients with relapsing multiple sclerosis.

Methods

Study design and participants

SYNERGY is a multicentre, randomised, double-blind, placebo-controlled, dose-ranging, parallel-group, phase 2 study implemented at 72 sites in 12 countries (appendix pp 6, 7). Eligible participants (aged 18–58 years) had an Expanded Disability Status Scale (EDSS) score of 2–6 and relapsing multiple sclerosis, including relapsing-remitting multiple sclerosis and secondary progressive multiple sclerosis with relapses. Evidence of clinical or neuroimaging disease activity was required within 12 months before enrolment. For participants with relapsing-remitting multiple sclerosis, occurrence of at least two of the following three events was required: clinical relapse, gadolinium-positive lesions, and new T2 lesions on MRI of the brain or spinal cord. For participants with secondary progressive multiple sclerosis with relapses, occurrence of at least one of the following two events was required: clinical relapse and gadolinium-positive lesions on MRI of the brain or spinal cord. A stable pretreatment EDSS score—ie, 0·5 point difference or less in scores between screening (day –28 to day –1) and baseline (randomisation, day 1)—was also required. However,

participants were not required to have received immunomodulatory disease-modifying treatment for multiple sclerosis (including interferon beta) before randomisation. Key exclusion criteria were: the Timed 25-Foot Walk (T25FW) longer than 30 s at screening; a multiple sclerosis relapse that occurred within 90 days before baseline, or not yet stabilised before screening, or both; treatment with fingolimod or natalizumab within 3 months of baseline; treatment with alemtuzumab, ocrelizumab, or rituximab within 6 months of baseline; and treatment with steroids within 30 days of baseline. A full list of inclusion and exclusion criteria is available in the appendix (pp 3, 4).

The study was undertaken in accordance with the International Conference on Harmonisation Good Clinical Practice (GCP) guidelines, European directives regarding clinical trials and investigational medicinal products, and the Declaration of Helsinki. All investigators obtained the required approvals from independent ethics committees and institutional review boards. All participants provided written informed consent.

Randomisation and masking

After screening for the study, eligible participants were randomly allocated in a 1:2:2:2:2 ratio to one of five parallel treatment groups of opicinumab (3 mg/kg, 10 mg/kg, 30 mg/kg, or 100 mg/kg) or placebo, using a centralised interactive voice and web response system (Bracket Global, Boston, MA, USA). Randomisation was stratified by type of multiple sclerosis (relapsing-remitting multiple sclerosis or secondary progressive multiple sclerosis with relapses) and region (North America, eastern Europe, or western Europe). All participants and study staff, except pharmacists or the designee who was responsible for preparing the study treatments, were masked to study treatment. Masking was achieved by infusing the same volume over the same duration regardless of treatment group.

Procedures

Participants received an intravenous infusion of opicinumab (3 mg/kg, 10 mg/kg, 30 mg/kg, or 100 mg/kg) or placebo (sterile 0·9% normal saline) once every 4 weeks starting on day 1 after randomisation for a total of 19 doses over 72 weeks (appendix p 23). All participants self-administered intramuscular interferon beta-1a (30 µg open-label) once a week from baseline to week 84 as background disease-modifying treatment to control CNS inflammation.

Key clinical assessments included EDSS score, T25FW, dominant and non-dominant hand Nine-Hole Peg Test (9HPT), and the 3 s Paced Auditory Serial Addition Test (PASAT-3), and these were done every 12 weeks and at unscheduled visits for suspected relapses. At the discretion of the investigator, treatment of relapses with steroids was permitted. Brain MRI was done every 4 weeks between baseline and week 24, then at weeks 48, 72, and 84. MRI scans were analysed centrally by NeuroRx (Montreal, QC, Canada). MRI protocol and analysis procedures are described in the appendix (pp 4, 5, 8–15).

Outcomes

The primary endpoint was the percentage of participants in the intention-to-treat population with confirmed improvement from baseline of neurophysical function, cognitive function, or both over 72 weeks of treatment. Confirmed improvement was defined as meeting one or more of the following five criteria, sustained for 12 weeks or longer: at least a 1-point decrease from baseline in EDSS score, or at least a 15% improvement from baseline in either T25FW, dominant or non-dominant hand 9HPT, or PASAT-3. The primary endpoint did not take into account disability progression that might occur on different components of the endpoint.

The secondary endpoint was the percentage of participants in the intention-to-treat population with 12-week confirmed worsening of neurophysical function, cognitive function, or both compared with baseline over 72 weeks. Confirmed worsening was defined as meeting one or more of the following six criteria, sustained for 12 weeks or longer: at least a 1-point increase in EDSS score from a baseline score of 5·5 or less; at least a 0·5-point increase in EDSS score from a baseline score of 6; or at least a 15% worsening from baseline in T25FW, dominant or non-dominant hand 9HPT, or PASAT-3.

A sensitivity analysis was done in the per-protocol population of responses to individual components of the primary endpoint. Subgroup analyses were done in the intention-to-treat population based on baseline demographics (age and region), clinical characteristics (EDSS score, type of multiple sclerosis, multiple sclerosis treatment history, and disease duration), and MRI characteristics (whole-brain magnetisation transfer ratio [MTR] and diffusion tensor imaging radial diffusivity [DTI-RD], thalamic volume, whole brain volume, and gadolinium-positive lesion count), dichotomised at the median (except categorical variables). Sensitivity and subgroup analyses were prespecified in the Statistical Analysis Plan before study database lock on May 9, 2016.

A tertiary endpoint prespecified in the Statistical Analysis Plan and analysed in the intention-to-treat population was the overall response score, which integrated assessments of disability improvement and worsening over time using repeated measures (appendix p 24). The overall response score encompassed all disability components included in the primary and secondary endpoints, other than PASAT-3, with the same thresholds for improvement or worsening. At every study visit, component assessments were given a score of either –1, 0, or 1 versus baseline. A score of –1 was a change that met the worsening threshold, a score of 0 was no change or a subthreshold change, and a score of 1 was a change that met the improvement threshold. Scores from the four assessments were summed at every scheduled visit, with the overall response score ranging from 4 (improvement

in all components) to –4 (worsening in all). Raw values for the 9HPT, T25FW, and PASAT-3 were used in all efficacy analyses.

Exploratory endpoints included MRI measures in new or pre-existing brain lesions with conventional and non-conventional sequences (eg, changes from baseline in MTR and DTI-RD for pre-existing T2 lesions)[14] and whole-brain volume. Imaging sequences were standardised across scanners and sites (appendix p 5). Pharmacokinetic analyses were done based on predose and post-dose concentrations in serum of opicinumab, which we obtained at baseline (day 1) and at weeks 4, 8, 16, 24, 36, 48, 60, and 72, and at the end-of-study or early termination visit.

For more on **MedDRA** see https://www.meddra.org

Adverse events and serious adverse events were assessed and recorded (using MedDRA codes) by treating clinicians at the investigational sites, from the first dose of study treatment and from screening, respectively, until the end of the study at week 84. Safety assessments were done in the intention-to-treat population and included physical examination, vital signs, bodyweight, 12-lead electrocardiogram (ECG), clinical and brain MRI assessments for multiple sclerosis disease activity, Columbia Suicide Severity Rating Scale (C-SSRS), haematology, blood chemistry, urinalysis, and serum antibodies to opicinumab.

Statistical analysis

We planned to enrol 396 participants in the study with 88 patients per treatment group, except for the 3 mg/kg opicinumab group which would have half this number (n=44). Based on unpublished clinical trial data from our previous work using intramuscular interferon beta-1a, we predicted that about 42% of participants in the placebo group (ie, those receiving intramuscular interferon beta-1a as background disease-modifying treatment) would attain a 12-week confirmed disability improvement over 72 weeks. The 3 mg/kg, 10 mg/kg, 30 mg/kg, and 100 mg/kg opicinumab groups were predicted to have a corresponding therapeutic δ 5%, 20%, 30%, and 45% better than placebo, respectively. A sample size of 88 participants per treatment group was used to detect a linear trend with about 80% power using a one-sided Cochran-Armitage test at the 0·05 significance level, assuming a monotonic treatment response and 15% dropout rate. The linear trend test was chosen to provide higher statistical power.

The intention-to-treat population comprised all participants who received at least one dose of study treatment. Efficacy analyses were done in the intention-to-treat population minus six dosed participants (n=2 placebo, n=4 opicinumab) from two sites with GCP violations who were prospectively excluded because of potential unblinding events. The prespecified per-protocol population consisted of patients who received 80% or more of the 19 planned doses of treatment.

Analyses of primary and secondary efficacy endpoints were done using logistic regression models, with type of multiple sclerosis, geographical region, baseline EDSS score, T25FW time, time for the non-dominant hand and dominant hand 9HPT (average of the two hands), and PASAT-3 score as covariates, and with treatment group as the classification variable. Odds ratios (ORs) of improvement or worsening of each active treatment group versus placebo were derived from the model. A hierarchical testing sequence was used with a linear trend test done across doses, based on the model, at a significance level of 0·05 (two-sided), followed by comparison of each active dose group versus placebo, also based on the model. Nominal p values, however, were provided for illustration purposes, even when the linear trend test did not reach significance. Subgroup analyses were done similarly, using logistic regression models. Time to confirmed improvement and worsening were determined using a Cox proportional hazards model; similar analyses were done on each of the individual components.

A systematic, multivariate, post-hoc analysis anchored on the overall response score was done to identify demographic and baseline predictors of opicinumab treatment response. Baseline candidate covariates included nine demographic and clinical characteristics and 13 MRI characteristics (appendix p 5). Multivariate repeated-measure mixed models with stepwise model selection were used to identify treatment response predictors. The likelihood ratio test was used to select significant predictors and a numerical grid search was done to identify optimum cutoff values. The robustness of identified subpopulations was assessed on the primary and secondary endpoints, the overall response score, and MRI parameters.

Safety data were reported for each treatment group and for opicinumab overall. Any adverse event with a missing onset date and a resolution date falling after the first dose of study treatment was considered treatment-emergent.

We used SAS version 9.4 (TS1M2) for all statistical analyses. This study was registered with ClinicalTrials.gov, number NCT01864148.

Role of the funding source

The funder contributed to study design, study implementation, data analysis, data interpretation, and writing of the report. The report was written by medical writers who were paid by the funder. The funder also contributed to the decision to submit for publication. All authors had full access to study data, had full editorial control, and approved the final version. The corresponding author had final responsibility for the decision to submit for publication.

Results

The study was done between Aug 13, 2013, and March 29, 2016. Between study initiation and July 31, 2014, 533 patients were screened for the study, of whom 419 were randomly allocated either placebo or one of the doses of opicinumab (figure 1). 418 patients received at least one dose of study treatment and comprised the intention-to-treat population. Placebo was assigned to 93 patients

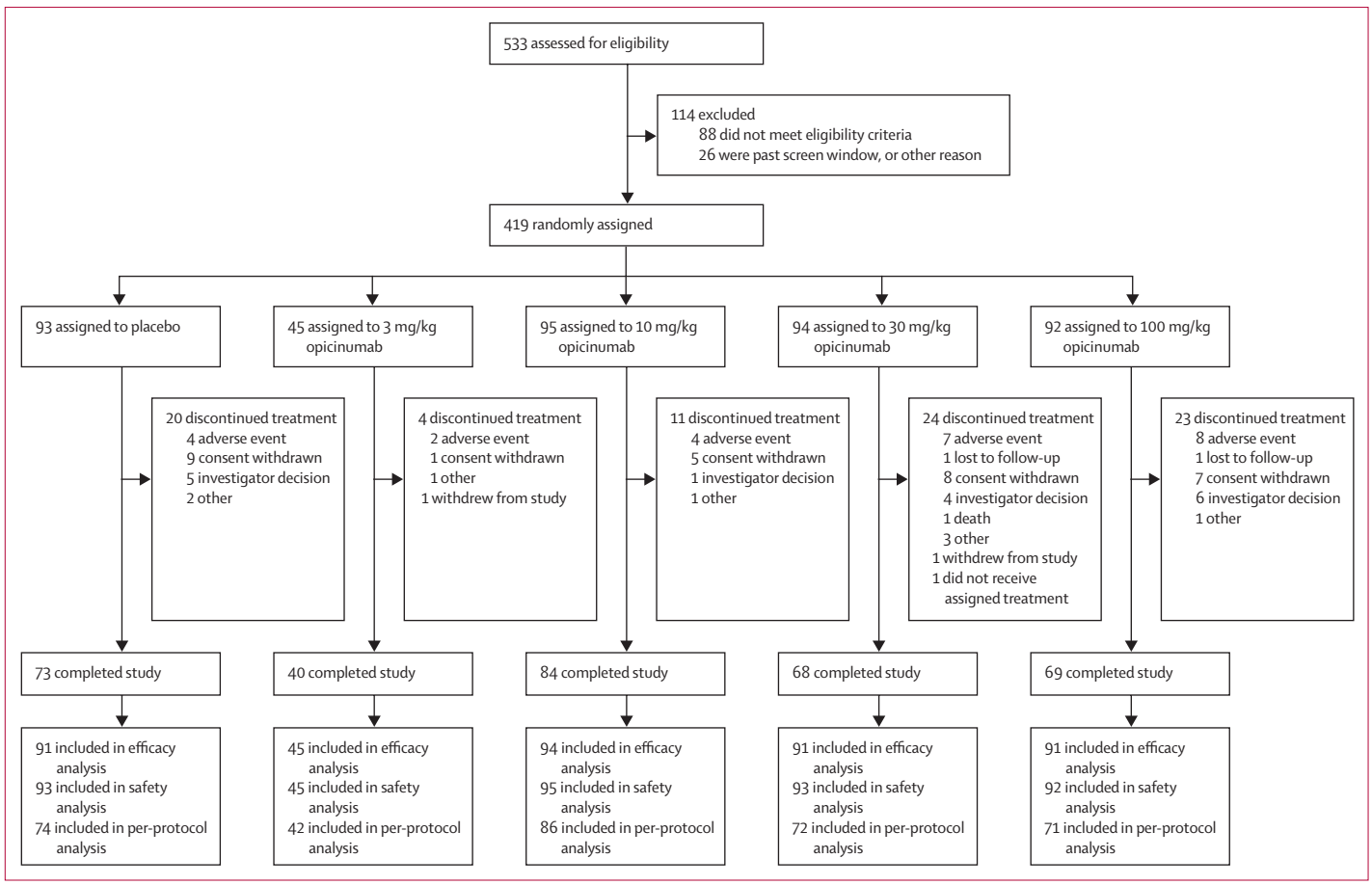

Figure 1: **Trial profile**

and opicinumab to 325 participants (doses given were 3 mg/kg [n=45], 10 mg/kg [n=95], 30 mg/kg [n=93], and 100 mg/kg [n=92]). Baseline demographic and multiple sclerosis-related characteristics in the intention-to-treat population were generally comparable across treatment groups (table 1). In the intention-to-treat population, 192 (46%) patients had not received any immunomodulatory multiple sclerosis treatment (including interferon beta) before randomisation. Pharmacokinetic results showed that concentrations in plasma of opicinumab reached steady state after about 16 weeks, with a dose-proportional increase in exposure (appendix p 27).

334 (80%) of 418 participants completed the study. Six patients (two assigned placebo and four assigned any dose of opicinumab) from two study sites were prospectively excluded from efficacy analyses because of violations of GCP that were potential unblinding events; therefore 412 individuals were included in efficacy analyses. The per-protocol population comprised 345 (83%) of 418 participants who received 80% or more of the 19 planned doses of treatment.

Compared with baseline, confirmed disability improvement over 72 weeks (the primary endpoint) was recorded in 45 (49%) of 91 participants assigned to placebo, 21 (47%) of 45 assigned to opicinumab 3 mg/kg, 59 (63%) of 94 assigned to opicinumab 10 mg/kg, 59 (65%) of 91 assigned to opicinumab 30 mg/kg, and 36 (40%) of 91 assigned to opicinumab 100 mg/kg (figure 2). The estimated proportion of confirmed improvement responders based on logistic regression was 0·516 in the placebo group, and was 0·511, 0·656, 0·688, and 0·412 in the opicinumab 3 mg/kg, 10 mg/kg, 30 mg/kg, and 100 mg/kg groups, respectively. Compared with placebo, disability improvement did not differ with 3 mg/kg opicinumab (OR 0·98, 95% CI 0·46–2·07; p=0·96) or 100 mg/kg opicinumab (0·66, 0·36–1·21; p=0·18), with weak evidence of improvement seen with 10 mg/kg opicinumab (1·79, 0·97–3·31; p=0·064) and some improvement with 30 mg/kg opicinumab (2·06, 1·11–3·84; p=0·022). No significant treatment effect of opicinumab versus placebo was seen with the linear trend test across dosing groups (p=0·89). Findings of the prespecified sensitivity analysis of the primary endpoint showed results in the per-protocol population were similar to those in the intention-to-treat population (appendix p 26).

Compared with placebo, no effect on confirmed worsening in disability over 72 weeks was recorded with opicinumab in the intention-to-treat population (linear

	Placebo (n=93)	3 mg/kg opicinumab (n=45)	10 mg/kg opicinumab (n=95)	30 mg/kg opicinumab (n=93)	100 mg/kg opicinumab (n=92)
Female	67 (72%)	24 (53%)	59 (62%)	61 (66%)	66 (72%)
Male	26 (28%)	21 (47%)	36 (38%)	32 (34%)	26 (28%)
Age (years)	40 (33–46)	35 (30–42)	42 (35–47)	43 (33–48)	39 (33–47)
Weight (kg)	71 (58–84)	67 (61–81)	69 (60–83)	70 (62–81)	72 (63–83)
Any previous disease-modifying treatment*	52 (56%)	29 (64%)	47 (49%)	50 (54%)	48 (52%)
Glatiramer acetate	20 (22%)	8 (18%)	14 (15%)	17 (18%)	13 (14%)
Intramuscular interferon beta-1a	9 (10%)	7 (16%)	11 (12%)	15 (16%)	7 (8%)
Subcutaneous interferon beta-1b	8 (9%)	6 (13%)	6 (6%)	11 (12%)	10 (11%)
EDSS score	3·5 (2·5–4·5)	3·0 (2·0–4·0)	2·8 (2·0–4·5)	3·5 (2·0–4·5)	3·0 (2·0–4·5)
Disease duration (years)†	9·0 (3·0–19·0)	7·0 (3·0–12·0)	9·0 (3·0–16·0)	9·0 (4·0–16·0)	6·5 (3·0–15·0)
Relapsing-remitting multiple sclerosis	73 (78%)	37 (82%)	73 (77%)	74 (80%)	73 (79%)
Number of relapses in previous year	1·4 (0·7)	1·5 (0·7)	1·4 (0·7)	1·5 (0·7)	1·5 (0·7)
T2 lesion volume (mL)	12·4 (14·8)	12·9 (15·3)	10·2 (12·9)	10·5 (12·6)	12·5 (15·1)
Gadolinium-positive lesions					
0	54 (58%)	25 (56%)	56 (59%)	49 (53%)	54 (59%)
1–2	21 (23%)	15 (33%)	25 (26%)	26 (28%)	25 (27%)
3–4	4 (4%)	1 (2%)	5 (5%)	4 (4%)	5 (5%)
5–8	7 (8%)	2 (4%)	5 (5%)	10 (11%)	2 (2%)
>8	7 (8%)	2 (4%)	4 (4%)	4 (4%)	6 (7%)
Normalised brain volume (mL)	1422·5 (85·8)	1442·0 (96·4)	1415·3 (85·8)	1416·8 (91·3)	1410·2 (85·8)
Whole brain MTR (nMTRu)‡	0·2 (0·2)	0·2 (0·3)	0·25 (0·2)	0·3 (0·2)	0·2 (0·3)
Whole brain DTI-RD ($\times 10^{-3}$ mm²/s)§	0·7 (0·04)	0·74 (0·05)	0·7 (0·04)	0·7 (0·04)	0·7 (0·05)

Data are n (%), mean (SD), or median (IQR). EDSS=Expanded Disability Status Scale. MTR=magnetisation transfer ratio. nMTRu=normalised MTR units. DTI-RD=diffusion tensor imaging radial diffusivity. *Treatments used by ≥10% of the opicinumab population are reported. †Duration since symptom onset. ‡n=90 for placebo, n=43 for 3 mg/kg opicinumab, n=94 for 10 mg/kg opicinumab, n=93 for 30 mg/kg opicinumab, and n=91 for 100 mg/kg opicinumab. §n=89 for placebo, n=43 for 3 mg/kg opicinumab, n=91 for 10 mg/kg opicinumab, n=87 for 30 mg/kg opicinumab, and n=89 for 100 mg/kg opicinumab.

Table 1: **Baseline demographic, clinical, and MRI characteristics (intention-to-treat population)**

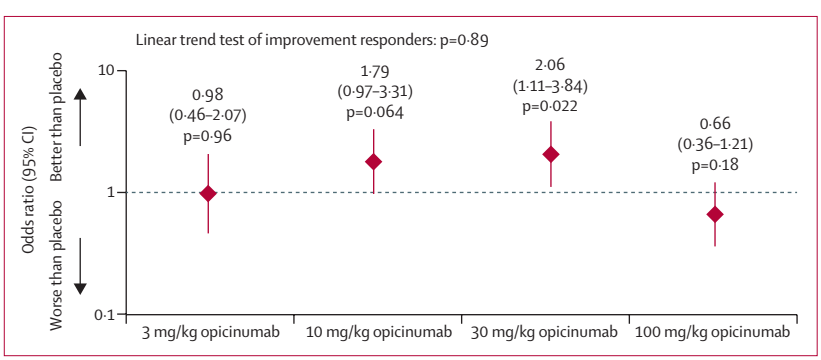

Figure 2: **Participants with confirmed disability improvement (multicomponent primary endpoint)**
The odds ratio versus placebo associated with the estimated proportion of confirmed improvement responders was determined in the intention-to-treat population minus six participants with violations of Good Clinical Practice.

trend test, p=0·53; appendix p 25) or in the per-protocol population (appendix p 26).

Overall, the incidence and severity of adverse events was similar for the placebo and opicinumab groups (all doses combined and for each opicinumab dosing group; table 2; appendix pp 18–21). Adverse events occurred in 79 (85%) patients assigned placebo and in 275 (85%) patients assigned any dose of opicinumab. Adverse events related to treatment were recorded in eight (9%) of 93 participants who received placebo and 51 (16%) of 325 participants who received any dose of opicinumab. The most frequent adverse events in the total opicinumab group included influenza-like illness (140 [43%] *vs* 37 [40%] with placebo), multiple sclerosis relapses (117 [36%] *vs* 30 [32%]), and headache (51 [16%] *vs* 23 [25%]). Adverse events reported in 2% or more of participants receiving any dose of opicinumab were pyrexia (40 [12%] *vs* seven [8%]), increased alanine aminotransferase (20 [6%] *vs* three [3%]), increased aspartate aminotransferase (12 [4%] *vs* one [1%]), insomnia (17 [5%] *vs* one [1%]), pharyngitis (15 [5%] *vs* two [2%]), and menorrhagia (eight [2%] *vs* 0 [0%]). The frequency of liver function tests over three times the upper limit of normal after baseline was similar between placebo and opicinumab (total) groups, without any dose dependence (data not shown).

The frequency of serious adverse events (table 2; appendix p 22) and treatment discontinuations because of adverse events was similar between the placebo and opicinumab (all doses combined) groups; however, discontinuations were higher with opicinumab 30 mg/kg and 100 mg/kg doses than with 3 mg/kg and 10 mg/kg doses. Serious adverse events reported as related to treatment were urinary tract infection in one (1%) participant in the the placebo group, suicidal ideation and intentional overdose in one (1%) participant in the 30 mg/kg opicinumab group, bipolar disorder in one (1%)

	Placebo (n=93)	Opicinumab, all doses (n=325)	3 mg/kg opicinumab (n=45)	10 mg/kg opicinumab (n=95)	30 mg/kg opicinumab (n=93)	100 mg/kg opicinumab (n=92)
Adverse event	79 (85%)	275 (85%)	39 (87%)	84 (88%)	79 (85%)	73 (79%)
Treatment-related adverse event	8 (9%)	51 (16%)	8 (18%)	15 (16%)	12 (13%)	16 (17%)
Intramuscular interferon beta-1a-related adverse event	51 (55%)	190 (58%)	28 (62%)	58 (61%)	54 (58%)	50 (54%)
Serious adverse event	13 (14%)	51 (16%)	4 (9%)	11 (12%)	20 (22%)	16 (17%)
Treatment-related serious adverse event*	1 (1%)	6 (2%)	0	0	1 (1%)	5 (5%)
Hypersensitivity	0	4 (1%)	0	0	0	4 (4%)
Urinary tract infection	1 (1%)	0	0	0	0	0
Bipolar disorder	0	1 (<1%)	0	0	0	1 (1%)
Suicidal ideation†	0	1 (<1%)	0	0	1 (1%)	0
Intentional overdose†	0	1 (<1%)	0	0	1 (1%)	0
Intramuscular interferon beta-1a-related serious adverse event	1 (1%)	3 (<1%)	0	0	2 (2%)	1 (1%)
Treatment discontinuation because of adverse event	4 (4%)	20 (6%)	2 (4%)	3 (3%)	7 (8%)	8 (9%)
Study withdrawal because of adverse event	4 (4%)	21 (6%)	2 (4%)	4 (4%)	8 (9%)	7 (8%)
Adverse events by severity						
Mild	20 (22%)	73 (22%)	13 (29%)	25 (26%)	20 (22%)	15 (16%)
Moderate	52 (56%)	181 (56%)	24 (53%)	53 (56%)	53 (57%)	51 (55%)
Severe	7 (8%)	21 (6%)	2 (4%)	6 (6%)	6 (6%)	7 (8%)
Adverse event ≥10% in any group by preferred term‡						
Influenza-like illness	37 (40%)	140 (43%)	17 (38%)	51 (54%)	34 (37%)	38 (41%)
Multiple sclerosis relapse	30 (32%)	117 (36%)	18 (40%)	35 (37%)	36 (39%)	28 (30%)
Headache	23 (25%)	51 (16%)	8 (18%)	19 (20%)	13 (14%)	11 (12%)
Upper respiratory tract infection	13 (14%)	45 (14%)	4 (9%)	21 (22%)	11 (12%)	9 (10%)
Urinary tract infection	13 (14%)	43 (13%)	7 (16%)	14 (15%)	9 (10%)	13 (14%)
Pyrexia	7 (8%)	40 (12%)	9 (20%)	8 (8%)	12 (13%)	11 (12%)
Nasopharyngitis	16 (17%)	34 (10%)	3 (7%)	12 (13%)	8 (9%)	11 (12%)
Fatigue	8 (9%)	25 (8%)	6 (13%)	5 (5%)	7 (8%)	7 (8%)
Back pain	9 (10%)	24 (7%)	3 (7%)	9 (9%)	6 (6%)	6 (7%)
Fall	10 (11%)	18 (6%)	1 (2%)	4 (4%)	8 (9%)	5 (5%)
Pain in extremity	4 (4%)	18 (6%)	5 (11%)	5 (5%)	7 (8%)	1 (1%)
Pharyngitis	2 (2%)	15 (5%)	5 (11%)	4 (4%)	3 (3%)	3 (3%)
Diarrhoea	3 (3%)	14 (4%)	5 (11%)	3 (3%)	3 (3%)	3 (3%)

Data are number of participants (%). *Treatment-related serious adverse events were based on the judgment of the investigator. †Suicide ideation and intentional overdose occurred in one participant. ‡Participants were counted only once within every preferred term.

Table 2: **Summary of adverse events (intention-to treat population)**

participant in the 100 mg/kg opicinumab group, and hypersensitivity in four (4%) participants in the 100 mg/kg opicinumab group (table 2). All four hypersensitivity reactions were assessed as related to opicinumab; one event occurred on the first infusion and three occurred on the second infusion, with all events occurring less than 45 min from infusion start (three of four events were within 5 min). All four hypersensitivity reactions resolved with standard medical treatment but resulted in treatment discontinuation. The frequency of psychiatric adverse events was similar with placebo and opicinumab, with no evidence of increased frequency with higher doses of opicinumab (18 [19%] with placebo *vs* nine [20%], 19 [20%], 21 [23%], and 14 [15%] with opicinumab 3 mg/kg, 10 mg/kg, 30 mg/kg, and 100 mg/kg, respectively). One patient in the opicinumab 30 mg/kg group died during the study due to a traffic accident, which was not considered related to study treatment.

A dose-related increase in mean weight was noted with opicinumab treatment (appendix p 16). At week 72, mean weight changes from baseline were a loss of 0·49 kg (SD 3·27) in the placebo group and a gain of 1·38 kg (SD 3·82) in the total opicinumab group. Weight increase greater than 7% from baseline at any post-baseline visit occurred in seven (8%) participants in the placebo group and 85 (26%) participants in the total opicinumab group.

In prespecified sensitivity analyses, time to a confirmed disability improvement did not differ with opicinumab doses of 3 mg/kg, 10 mg/kg, or 100 mg/kg but there was some evidence for a difference with the 30 mg/kg dose

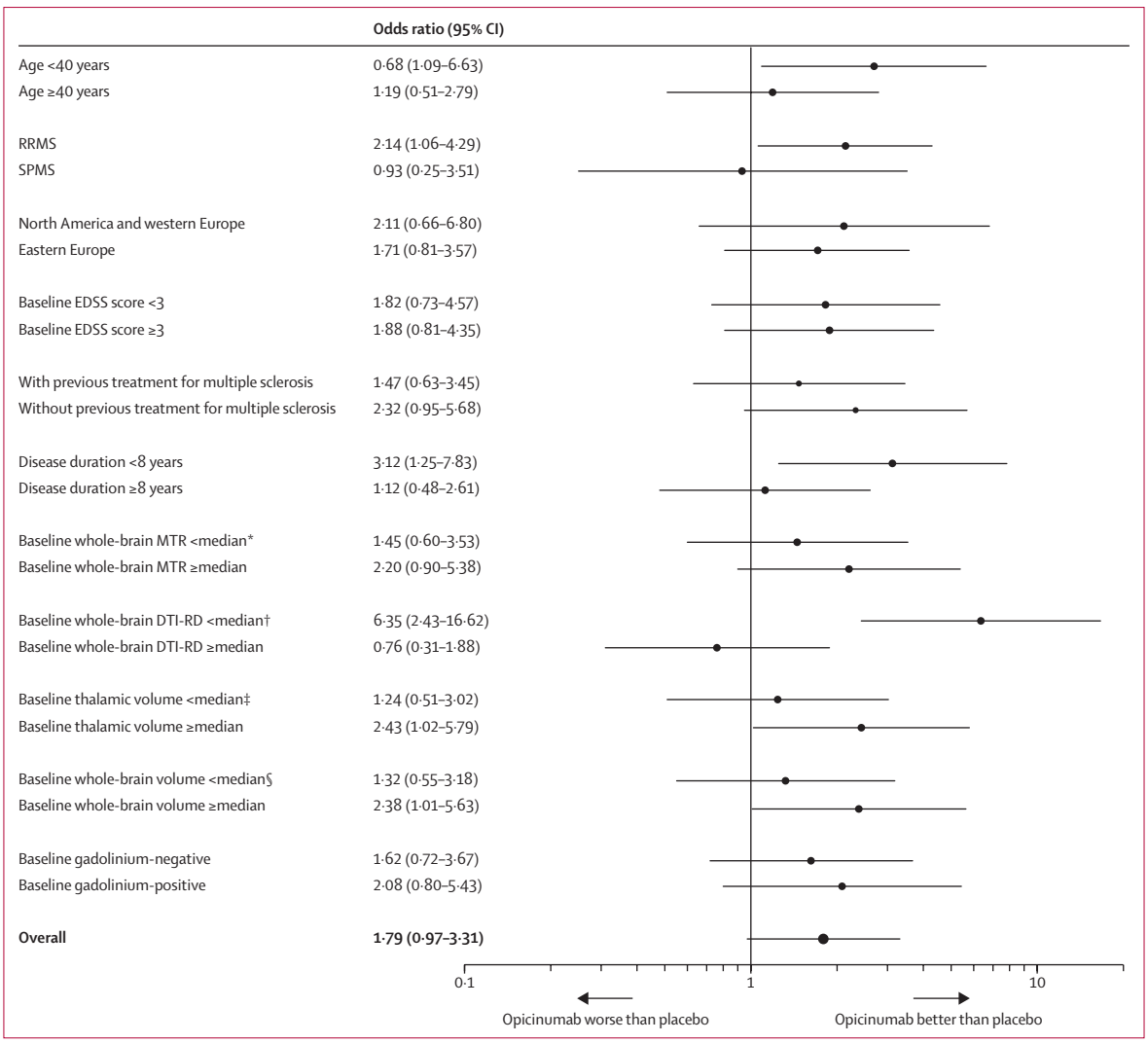

Figure 3: **Prespecified demographic, clinical, and MRI subgroup analyses of 10 mg/kg opicinumab versus placebo**
Analysis was based on logistic regression adjusted for type of multiple sclerosis, geographical region, and baseline component assessments. Prespecified characteristics were dichotomised at the median in the intention-to-treat population (except categorical variables). Whole-brain MTR and DTI-RD measures (not lesional measures) were presented. The median baseline value was used for all prespecified MRI subgroup analyses. RRMS=relapsing-remitting multiple sclerosis. SPMS=secondary progressive multiple sclerosis. EDSS=Expanded Disability Status Scale. MTR=magnetisation transfer ratio. DTI-RD=diffusion tensor imaging radial diffusivity. *Median baseline whole-brain MTR, 0·26 nMTRu. †Median baseline whole-brain DTI-RD, $0·73 \times 10^{-3}$ mm²/s. ‡Median baseline thalamic volume, 15·31 mL. §Median baseline whole-brain volume, 1419·94 mL.

compared with placebo (appendix p 28). The most uniformly positive response across the five individual components of the primary endpoint was observed in the 10 mg/kg opicinumab group but with only non-dominant hand 9HPT reaching nominal significance (appendix p 29). Other opicinumab dose responses varied across the individual components with each showing a negative response in at least one component. None of the opicinumab dosing groups showed consistent improvements across the five components of the secondary endpoint of worsening (appendix p 30).

In prespecified univariate subgroup analyses, there was some evidence that opicinumab 10 mg/kg was superior to placebo for confirmed disability improvement in participants with younger age (<40 years), with relapsing-remitting multiple sclerosis, with a shorter disease duration (<8 years), with lower baseline whole-brain DTI-RD ($<0·73 \times 10^{-3}$ mm²/s), with higher baseline thalamic volume (≥15·31 mL), and with higher baseline whole-brain volume (≥1419·94 mL; figure 3). In an exploratory analysis, MRI measures of disease activity—including gadolinium-positive lesion count and new or enlarging T2 lesion count over 72 weeks—appeared similar across treatment groups (appendix p 17).

The prespecified analysis of the overall response score showed improvements at week 24 and week 36 with all doses of opicinumab versus placebo, based on observed values (figure 4A). The 10 mg/kg group showed the largest

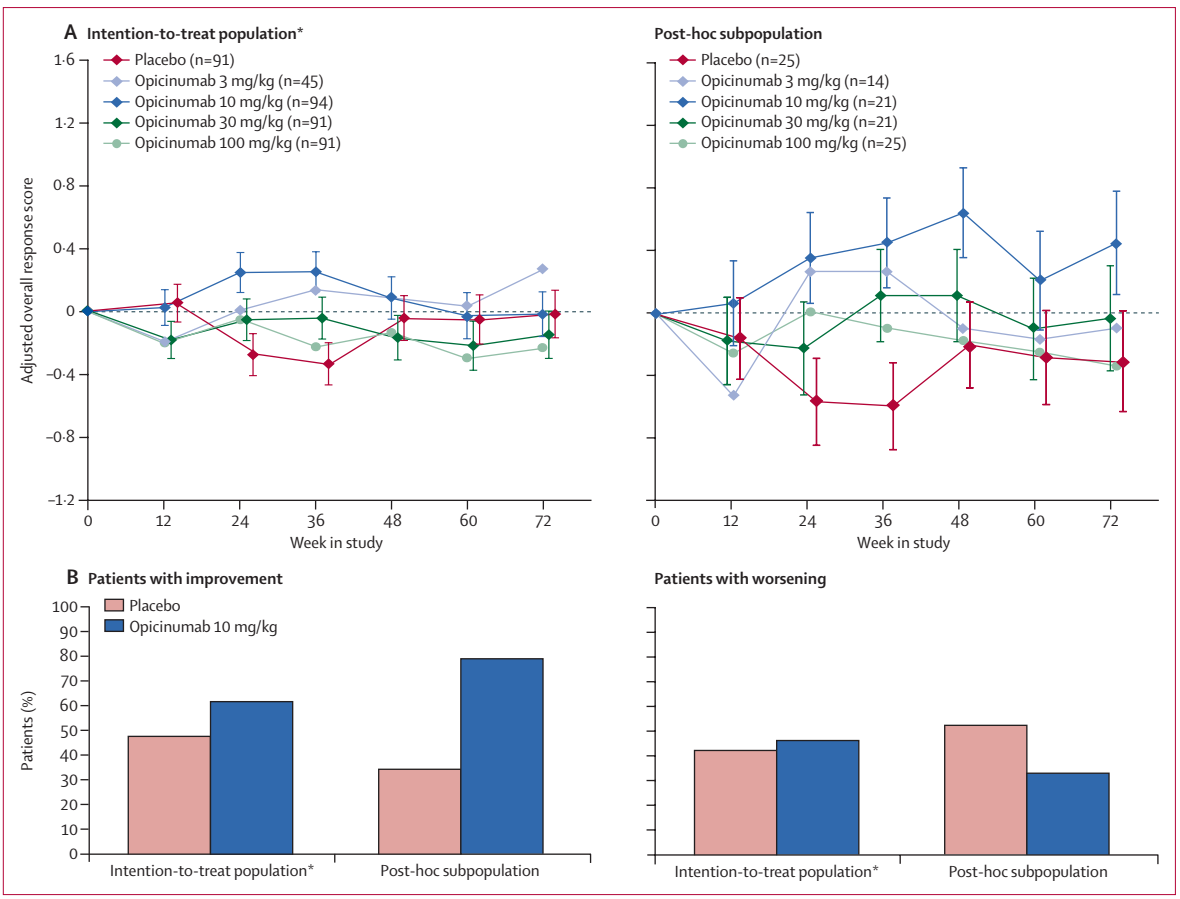

Figure 4: **Clinical outcomes in the intention-to-treat population and the subpopulation identified by systematic multivariate post-hoc analysis**
Mean (SE) overall response scores in intention-to-treat population and post-hoc subpopulation (A). Confirmed multicomponent endpoint improvement (primary endpoint) or worsening (secondary endpoint) with 10 mg/kg opicinumab (B). *Minus six participants with Good Clinical Practice violations who were prospectively excluded because of potential unblinding events.

improvement compared with placebo (baseline-adjusted mean score difference at week 24 was 0·52 [95% CI 0·19–0·85; p=0·0022] and at week 36 was 0·58 [0·25–0·92; p=0·0006]). Clinical effects waned after 36 weeks in most groups.

A post-hoc subpopulation (comprising roughly a quarter of patients in the intention-to-treat population) defined by three predictive baseline characteristics relative to the rest of the population—ie, shorter disease duration (≤20 years), lower mean baseline MTR in pre-existing non-enhancing brain T2 lesions (≤–0·31 nMTRu), and lower mean baseline DTI-RD in pre-existing non-enhancing brain T2 lesions (≤$0·95\times10^{-3}$ mm²/s)—was identified using a systematic multivariate post-hoc analysis of the overall response score (figure 4A). A numerically higher proportion of participants in this post-hoc subpopulation than in the SYNERGY inention-to-treat population had confirmed disability improvement by 72 weeks and a lower proportion had confirmed worsening with 10 mg/kg opicinumab (figure 4B). This post-hoc subpopulation showed potentially favourable changes in exploratory MRI biomarkers of CNS repair (appendix p 31). A post-hoc sensitivity analysis including PASAT-3 as a component in the overall response score suggested similar potential improvement with 10 mg/kg opicinumab versus placebo in the post-hoc identified population (appendix p 32). Because of the small sample size, no significance analysis was done on this identified subgroup.

Discussion

The findings of our randomised phase 2 study in patients with relapsing multiple sclerosis did not show a linear dose-related confirmed disability improvement with opicinumab versus placebo.

When the SYNERGY study was designed, there were substantial information gaps, including a lack of experience or no strong rationale to guide selection of subsets of patients likely to benefit from treatment, no information on the optimum dose of opicinumab (leading to a broad dose range and multiple dose groups), and no established methodology for measuring the clinical benefit of therapeutic CNS remyelination, necessitating inclusion of novel clinical endpoints. As a phase 2

learning study, SYNERGY data provide hypothesis-generating information about the patient population, dose, treatment duration, clinical efficacy endpoints, and imaging biomarkers that could be investigated further to assess their potential for evaluating neuroreparative candidate treatments in multiple sclerosis.

Inclusion criteria for the SYNERGY study were chosen to achieve two goals. First, we aimed to enrich the study population for patients with relatively recent demyelination before study participation. The study was done in patients with relapsing multiple sclerosis, based on hypotheses that more recent multiple sclerosis lesions should be easier to remyelinate owing to the greater preservation of axons and less interference from glial scarring[15,16] and that some degree of inflammation could be beneficial for myelin debris clearance and myelin repair.[17] Second, we aimed to ensure stable baseline disability assessments, because improvement and worsening in disability during the study were determined relative to baseline. We accomplished stable assessment with three enrolment criteria—ie, no relapse within 3 months before randomisation, no high-dose steroid treatment within 30 days before randomisation, and stable screening and baseline EDSS scores. Patients with EDSS scores of 2–6 were enrolled to assess the efficacy of opicinumab in improving pre-existing neurological deficits.

The relative contribution of chronic demyelination of surviving axons versus axonal transection to multiple sclerosis-related disabilities is unknown. During the design of the SYNERGY study, we assumed that chronic demyelination contributes broadly to multiple sclerosis disability, depending on lesion location, and that opicinumab could improve disability across various neurological functions. Accordingly, we selected a multicomponent endpoint capable of assessing potential therapeutic benefit across the seven neurological systems measured by the EDSS, in upper extremity function (9HPT), long-distance (EDSS 500 m walk) and short-distance (T25FW) ambulation, and cognitive function (PASAT-3). Two criteria were built into the primary endpoint to provide relative certainty and reduce noise—ie, a minimum threshold of change and the requirement for confirmation 12 weeks later. On the basis of internal data analysis, the 15% threshold of changes in Multiple Sclerosis Functional Composite components provided a good balance between sensitivity and specificity to capture improvement. Similar multicomponent disability endpoints such as EDSS-Plus[18] have been developed and applied in phase 3 trials of progressive multiple sclerosis.[19,20] It is noteworthy that analyses of confirmed disability improvement as well as overall response score were based on the comparison of assessments during the study with those at baseline; the outcomes would, therefore, not be affected by relapse recovery during the study.

The primary analysis of the SYNERGY study, which tested a monotonic, linear, dose response to opicinumab on confirmed disability improvement, did not show a treatment effect over 72 weeks. The 10 mg/kg and 30 mg/kg opicinumab groups showed some effect in favour of opicinumab versus placebo. A sigmoid dose–response curve for histological remyelination has been noted in the local demyelination model in rat spinal cord induced by injecting lysolecithin with maximum response at opicinumab 10 mg/kg (intraperitoneal single dose ranged from 0·1 mg/kg to 100 mg/kg).[21] Moreover, in the phase 1 multiple ascending dose study, the 3 mg/kg and 10 mg/kg doses of opicinumab in patients with multiple sclerosis were estimated to result in CNS concentrations corresponding to the EC_{50} (effective concentration to achieve 50% response) and EC_{90}, respectively, of maximum remyelinating response in the rat lysolethicin demyelination model.[22]

The 100 mg/kg opicinumab dose did not show a favourable response. CNS toxicity with this dose of opicinumab is unlikely because we did not note an increase in neurological adverse events. High-dose opicinumab might result in rapid onset of differentiation of oligodendrocyte precursor cells before they migrate into demyelinated lesions. If oligodendrocyte precursor cells differentiate before finding axons to myelinate, they could undergo apoptosis.[23] Furthermore, non-specific targeting effects at the highest dose of opicinumab are possible. Because the randomised phase 2 RENEW study[12] only assessed opicinumab at 100 mg/kg, the findings did not inform the optimum clinical dose of opicinumab for assessment in relapsing multiple sclerosis. The possibility that the more favourable responses at 10 mg/kg and 30 mg/kg were due to noise also remains to be ruled out.

Prespecified univariate subgroup analyses suggested some evidence that participants at a younger age with shorter disease duration and clinical and MRI features suggestive of more preserved brain tissue (eg, lower whole brain DTI-RD, higher whole-brain volume, and higher thalamic volume) responded better to opicinumab. The efficiency of myelin repair by oligodendrocytes declines during ageing, possibly because of fewer oligodendrocyte precursor cells or impaired recruitment of these cells to demyelinated axons at the lesion site.[24,25] The potentially increased disability improvement seen in participants with shorter disease duration could be associated with younger age, less axonal loss due to shorter duration of demyelination, the presence of a higher number of oligodendrocyte precursor cells because of fewer cycles of demyelination–remyelination events,[26] or fewer glial scars composed of reactive astrocytes and microglia that release factors detrimental to the recruitment and differentiation of oligodendrocyte precursor cells (eg, semaphorin 3A, netrin 1, ephrin B3, and chondroitin sulphate proteoglycans).[3] The relatively well-preserved brain structure suggested by higher baseline whole-brain volume and lower whole-brain DTI-RD are consistent with better preservation of CNS axons—a prerequisite for myelin repair.

A subgroup analysis of the RENEW study[27] showed a higher treatment benefit of opicinumab versus placebo in participants older than the median age at baseline (≥33 years). This finding could be accounted for by a higher rate of spontaneous recovery in visual evoked potential latency in patients younger than 33 years, which could pose a ceiling effect to the benefit of opicinumab treatment in this subpopulation. Moreover, because fewer patients older than 40 years (13%) were enrolled in the RENEW study compared with SYNERGY (47%), the negative effect of ageing on the remyelination potential of opicinumab might be less obvious.

The results of the prespecified analysis of overall response score showed that any potential benefits over placebo with 10 mg/kg opicinumab waned after 36 weeks. It is possible that any initial remyelination facilitated by opicinumab treatment was subsequently lost by new or recurrent inflammation. In the early stages of multiple sclerosis, remyelination occurs in lesions but it can be unstable or short-lived, probably because these lesions are persistently active or subjected to repeated cycles of demyelination and remyelination.[28]

A subpopulation defined by disease duration of 20 years or shorter and lower mean baseline MTR and DTI-RD in pre-existing brain T2 lesions identified by multivariate post-hoc analysis of the overall response score potentially had a greater and more durable treatment effect than all participants with a 10 mg/kg dose of opicinumab. Because the lipid content of myelin strongly affects MTR,[29] lower MTR in multiple sclerosis lesions could indicate more severe demyelination.[30] DTI-RD is thought to represent the diffusion of water molecules perpendicular to axonal fibre tracts and, therefore, is a potential marker for neural tissue damage.[31] Thus, multiple sclerosis lesions with lower DTI-RD could reflect more intact tissue structures relative to other multiple sclerosis lesions. Therefore, the multivariate analysis might have empirically identified a subset of patients with a combination of myelin loss but preserved axons, providing a substrate for the beneficial effects of remyelination treatment.[3] Although MTR is typically lower and DTI-RD is typically higher in multiple sclerosis lesions relative to normal-appearing brain tissue, in the multivariate analysis, lower MTR and DTI-RD are defined relative to other T2 lesions at baseline. In the SYNERGY study, baseline MTR and DTI-RD within T2 lesions were only moderately correlated at baseline (data not shown), suggesting the two techniques could reflect both overlapping and different aspects of lesion pathology. Since the biological significance and specificity of lesional MTR and DTI are still being investigated, our interpretation will need to be confirmed in future studies.

Consistent with findings of the phase 1 opicinumab study[22] and phase 2 RENEW study,[12] SYNERGY phase 2 data showed that opicinumab was generally well tolerated. Of 499 participants who have been exposed to opicinumab in clinical studies so far, seven hypersensitivity reactions have occurred exclusively during infusion of the highest dose of 100 mg/kg; all events resolved after discontinuation of treatment.[12] The proportion of patients with post-baseline weight increase greater than 7% in SYNERGY (total opicinumab group 26% *vs* placebo 8%) were similar to those in the RENEW study (total opicinumab group 32% *vs* placebo 10%).[12] The mechanism of opicinumab-related weight gain remains to be investigated.

Our study has several limitations. Because SYNERGY was a phase 2 dose-finding study, the sample size was selected on the basis of a linear dose-response assumption, and the primary hypothesis testing was done accordingly. Since the linear trend test failed to reject the null hypothesis, follow-up statistical tests for individual doses and subgroups and analyses of secondary and exploratory endpoints were subject to inflated type I error rates from multiple comparisons. Since SYNERGY was not a confirmatory phase 3 study, complex multiplicity control was not implemented and p values are, therefore, reported as nominal. All findings remain to be confirmed in future studies. Furthermore, the response rate in the placebo group was relatively high at 47%, which could be attributable to the considerable learning effect of PASAT-3 (which resulted in a 29% confirmed improvement in the placebo group based on PASAT-3 alone) or to the fact that 46% of the intention-to-treat population had not received any immunomodulatory disease-modifying treatment for multiple sclerosis before study entry and started background interferon beta-1a treatment simultaneously with study treatment. Whether this concurrent start of interferon beta-1a has confounded the study results is not determinable.

In conclusion, the SYNERGY primary analysis did not support a linear dose-response on confirmed disability improvement for opicinumab treatment versus placebo. The observations related to subpopulations that appear to be more responsive to opicinumab, and the unexpected dose-response relation, might generate hypotheses for testing in new studies of opicinumab and other remyelination treatments.

Contributors

DC contributed to the study concept and design, and was a study medical director. MM, BZ, and SIS were also study medical directors. RH, KRE, JD, GG, and H-PH were principal investigators. PAC contributed to study design. SM, SMG, and AD contributed to study design and study implementation. DLA and EF contributed to MRI data collection and MRI data interpretation. YC, JL, YZ, WC, LX, and IC contributed to the statistical analysis. All authors contributed to data analysis, data interpretation, and writing of the report. A full list of SYNERGY study investigators is provided in the appendix (pp 6, 7).

Declaration of interests

EF, RR, JL, YZ, WC, BZ, SMG, IC, and AD are employees of and hold stock or have stock options in Biogen. DC, MM, SM, YC, LX, and SIS are former employees of and hold stock in Biogen. RH has been an advisor, speaker, or consultant for Biogen, Merck Serono, Novartis, and Sanofi-Aventis and has received research support from Biogen and Merck Serono. KRE has received consulting fees from and speaker bureaus for Biogen, EMD Serono, and Genzyme and research support from Biogen, Genentech, Novartis, Pfizer, Envivo, Eisai, Eli Lilly, Vaccinex, and Sanofi-Genzyme. PAC has received consulting fees from Disarm Therapeutics and research support to his institution from

Annexon, Biogen, Genzyme, MedImmune, Novartis, and Sanofi. JD has been an advisor or speaker for Bayer HealthCare, Sanofi-Genzyme, Medis, Merck, Teva, and Roche and has received research support from the Ministry of Education and Science in Serbia (project no 175031). GG has served on advisory boards for AbbVie Biotherapeutics, Almirall, Atara Biotherapeutics, Biogen, Novartis, Merck, Merck Serono, Roche, Sanofi-Genzyme, and Teva, has received speaker fees from AbbVie Biotherapeutics, Biogen, Genzyme, Merck, Merck Serono, Sanofi-Genzyme, and Teva, and has received research support from Biogen, Genzyme, and Novartis. H-PH has received speaker fees and travel expenses from and served on steering committees and advisory boards for Bayer, Biogen, GeNeuro, Genzyme, MedImmune, Merck, Novartis, Octapharma, Receptos/Celgene, Roche, Sanofi, and Teva. DLA has received consulting fees from Acorda, Biogen, Roche, MedImmune, Mitsubishi, Novartis, Receptos, and Sanofi-Aventis, and grants from Biogen and Novartis.

Data sharing

For the **Clinical Data Request Portal** see www.biogenclinicaldatarequest.com

Requests for data should be submitted via our Clinical Data Request Portal. To gain access, data requestors will need to sign a data-sharing agreement. Data are made available for 1 year on a secure platform.

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