The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 19, 2017 VOL. 376 NO. 3

Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis

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ABSTRACT

BACKGROUND

An evolving understanding of the immunopathogenesis of multiple sclerosis suggests that depleting B cells could be useful for treatment. We studied ocrelizumab, a humanized monoclonal antibody that selectively depletes CD20-expressing B cells, in the primary progressive form of the disease.

METHODS

In this phase 3 trial, we randomly assigned 732 patients with primary progressive multiple sclerosis in a 2:1 ratio to receive intravenous ocrelizumab (600 mg) or placebo every 24 weeks for at least 120 weeks and until a prespecified number of confirmed disability progression events had occurred. The primary end point was the percentage of patients with disability progression confirmed at 12 weeks in a time-to-event analysis.

RESULTS

The percentage of patients with 12-week confirmed disability progression was 32.9% with ocrelizumab versus 39.3% with placebo (hazard ratio, 0.76; 95% confidence interval [CI], 0.59 to 0.98; P=0.03). The percentage of patients with 24-week confirmed disability progression was 29.6% with ocrelizumab versus 35.7% with placebo (hazard ratio, 0.75; 95% CI, 0.58 to 0.98; P=0.04). By week 120, performance on the timed 25-foot walk worsened by 38.9% with ocrelizumab versus 55.1% with placebo (P=0.04); the total volume of brain lesions on T_2-weighted magnetic resonance imaging (MRI) decreased by 3.4% with ocrelizumab and increased by 7.4% with placebo (P<0.001); and the percentage of brain-volume loss was 0.90% with ocrelizumab versus 1.09% with placebo (P=0.02). There was no significant difference in the change in the Physical Component Summary score of the 36-Item Short-Form Health Survey. Infusion-related reactions, upper respiratory tract infections, and oral herpes infections were more frequent with ocrelizumab than with placebo. Neoplasms occurred in 2.3% of patients who received ocrelizumab and in 0.8% of patients who received placebo; there was no clinically significant difference between groups in the rates of serious adverse events and serious infections.

CONCLUSIONS

Among patients with primary progressive multiple sclerosis, ocrelizumab was associated with lower rates of clinical and MRI progression than placebo. Extended observation is required to determine the long-term safety and efficacy of ocrelizumab. (Funded by F. Hoffmann–La Roche; ORATORIO ClinicalTrials.gov number, NCT01194570.)

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*A complete list of the investigators in the ORATORIO trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on December 21, 2016, at NEJM.org.

N Engl J Med 2017;376:209-20.
DOI: 10.1056/NEJMoa1606468

Primary progressive multiple sclerosis accounts for 10 to 15% of the overall population with multiple sclerosis.[1] The course of this disease differs from those of relapsing–remitting and secondary progressive forms of multiple sclerosis in that progression consists mainly of gradual worsening of neurologic disability from symptom onset, although relapses may occur.[1] Phase 3 trials in primary progressive multiple sclerosis have been unsuccessful,[2-4] and no disease-modifying treatments have been approved.

B cells contribute to the pathogenesis of multiple sclerosis, including the primary progressive form.[5] Although the mechanisms of tissue injury in multiple sclerosis are uncertain, B cells may influence pathogenesis through antigen presentation,[6] autoantibody production,[7,8] or cytokine secretion.[6] B cells are present in meningeal inflammation, which is characteristic of chronic multiple sclerosis and may cause adjacent cortical demyelinating and neurodegenerative pathologic features.[9,10]CD20 is a cell-surface antigen found on pre-B cells and mature and memory B cells but not on the earliest B-cell precursors or on plasma cells.[11-13] Ocrelizumab is a humanized monoclonal antibody that selectively depletes CD20-expressing B cells[14,15] while preserving the capacity for B-cell reconstitution and preexisting humoral immunity.[16,17]

A previous phase 2–3 trial of the chimeric monoclonal anti-CD20 antibody rituximab (OLYMPUS trial) in primary progressive multiple sclerosis did not meet its primary efficacy end point, but a subgroup analysis showed delayed progression of disability in younger patients (<51 years of age) with evidence of increased inflammatory disease activity.[3] Those results provided the rationale and in part informed the trial design for this investigation of ocrelizumab in patients with primary progressive multiple sclerosis. Here, we report results from a phase 3, randomized, parallel-group, double-blind, placebo-controlled trial (ORATORIO) that investigated the efficacy and safety of ocrelizumab in patients with primary progressive multiple sclerosis.

Methods

Trial Oversight

The sponsor, F. Hoffmann–La Roche, designed the trial in consultation with members of the ORATORIO trial steering committee. Data were collected by the investigators and analyzed by the sponsor; the results were reviewed by the sponsor and steering committee. An independent data and safety monitoring committee reviewed safety data on an ongoing basis and provided guidance on trial continuation, modification, or termination. (See the trial oversight section in the Supplementary Appendix, available with the full text of this article at NEJM.org.) All authors participated in the writing of the manuscript and approved the draft that was submitted for publication. The first draft of the manuscript was written by the first and last authors, with medical writing assistance funded by the sponsor. The authors vouch for the accuracy and completeness of the data and data analyses and for the fidelity of the trial to the protocol (available at NEJM.org). The trial was conducted in accordance with the provisions of the International Conference on Harmonisation Guidelines for Good Clinical Practice[18] and the Declaration of Helsinki.[19]

Patients

Key eligibility criteria were an age of 18 to 55 years, a diagnosis of primary progressive multiple sclerosis (according to the 2005 revised McDonald criteria),[20] a score on the Expanded Disability Status Scale (EDSS) of 3.0 to 6.5 at screening (range, 0 to 10.0, with higher scores indicating greater disability),[21] a score on the pyramidal functions component of the Functional Systems Scale of at least 2 (range, 0 to 6, with higher scores indicating greater disability), a duration of multiple sclerosis symptoms of less than 15 years in patients with an EDSS score of more than 5.0 at screening or less than 10 years in patients with an EDSS score of 5.0 or less at screening, and a documented history or the presence at screening of an elevated IgG index or at least one IgG oligoclonal band detected in the cerebrospinal fluid. Key exclusion criteria were a history of relapsing–remitting, secondary progressive, or progressive relapsing multiple sclerosis; contraindications to magnetic resonance imaging (MRI); contraindications to or unacceptable side effects from oral or intravenous glucocorticoids; and previous treatment with B-cell–targeted therapies and other immunosuppressive medications, as defined in the protocol.

Trial Design

Patients were randomly assigned in a 2:1 ratio to receive 600 mg of ocrelizumab by intravenous infusion (administered as two 300-mg infusions

14 days apart) or matching placebo every 24 weeks (Fig. S1 in the Supplementary Appendix). The trial was event-driven, such that double-blind treatment was administered for a minimum of five doses (120 weeks) until the occurrence in the trial cohort of approximately 253 events of disability progression that was confirmed for at least 12 weeks. Early enrollees in the trial received more than five double-blind doses, dependent on the time of enrollment and the number of confirmed disability progression events that had occurred (Table S1 in the Supplementary Appendix). All patients received intravenous methylprednisolone (100 mg) before infusion. Optional prophylaxis with analgesics or antipyretics and antihistamine was recommended before infusion, and adjustment of the infusion rate and symptomatic treatment during infusion were permitted to manage infusion-related reactions.

Randomization that was stratified according to geographic region and age was performed centrally by an independent interactive Web-response system. Each trial center had separate treating and examining investigators. An independent, trained investigator who was unaware of the trial-group assignments and was certified in administering the EDSS conducted the neurologic examination and scored the EDSS. EDSS assessment and data collection were captured with the use of a real-time, electronic tablet data-entry system. Multiple Sclerosis Functional Composite analysis was performed by the examining investigator or a qualified designee who was unaware of the trial-group assignments. MRI scans were analyzed independently at a central MRI reading center by staff members who were unaware of the trial-group assignments. (See the section on additional methodologic details in the Supplementary Appendix.)

Patients who completed the blinded treatment phase were eligible to enter the open-label extension phase of the trial, after the database lock and unblinding of trial results. Patients who discontinued prematurely or who did not wish to enter the open-label extension phase were included in the safety follow-up.

TRIAL END POINTS

The primary end point was the percentage of patients with disability progression confirmed at 12 weeks in a time-to-event analysis, in which disability progression was defined as an increase in the EDSS of at least 1.0 point from baseline that was sustained on subsequent visits for at least 12 weeks if the baseline score was 5.5 or less or an increase of at least 0.5 points that was sustained for at least 12 weeks if the baseline score was more than 5.5. If the primary end point reached a significance level of $P<0.05$, secondary end points were tested in the following hierarchical order as long as each preceding end point reached a significance level of $P<0.05$: the percentage of patients with disability progression confirmed at 24 weeks in a time-to-event analysis, change in performance on the timed 25-foot walk from baseline to week 120, change in the total volume of brain lesions on T_2-weighted MRI from baseline to week 120, change in brain volume from week 24 to week 120, and change in the Physical Component Summary score of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), version 2, from baseline to week 120 (range, 0 to 100, with higher scores indicating better physical-health–related quality of life. Drug safety and adverse events were also analyzed. There were 16 exploratory end points, including the time to onset of 12-week and 24-week confirmed composite disability progression (defined as the first confirmed occurrence of an increase in the EDSS score, an increase in the time to perform the timed 25-foot walk of ≥20%, or an increase in the time to complete the 9-hole peg test of ≥20%), time to a sustained increase of at least 20% in performance on the timed 25-foot walk, time to a sustained increase of at least 20% in the 9-hole peg test, total number of new or enlarging lesions on T_2-weighted images from baseline to week 120, and pharmacokinetics, immunogenicity, and pharmacodynamics of ocrelizumab.

STATISTICAL ANALYSIS

All efficacy end points were analyzed in the intention-to-treat population (all randomly assigned patients). The time to confirmed disability progression was analyzed with the use of a two-sided log-rank test for differences between the ocrelizumab and placebo groups that was stratified according to region (United States vs. rest of the world) and age (≤45 vs. >45 years) at baseline; a P value of less than 0.05 was considered to indicate statistical significance. Cox regression was used for estimation of hazard ratios. The sample size was based on an estimated rate of 12-week confirmed disability progression of 0.30 for the ocrelizumab group and 0.43 for the placebo group

over a period of 2 years (hazard ratio, 0.64). With a 2:1 ratio for randomization between the ocrelizumab and placebo groups, using a two-sided log-rank test, we calculated that a total sample of 630 patients would provide 80% statistical power to maintain a type I error rate of 0.01, assuming a dropout rate of approximately 20%. For the primary and first secondary efficacy end points (i.e., confirmed disability progression that was sustained for ≥12 weeks and ≥24 weeks, respectively), patients with missing data on the EDSS score at baseline were excluded from the analysis, and patients with an initial disability progression during the blinded treatment period who discontinued ocrelizumab or placebo early and did not have a subsequent visit with confirmatory measurement of the EDSS score were considered to have confirmed disability progression (Table S2 in the Supplementary Appendix). Hierarchical testing of each secondary efficacy end point was performed. (For details, see the Statistical Analysis section in the Supplementary Appendix.)

Data for the timed 25-foot walk and the volume of lesions on T_2-weighted images often are not normally distributed, with potentially extreme outlier values. Therefore, the use of the ranked analysis of covariance (ANCOVA) method was prespecified to perform robust hypothesis testing. Missing values were imputed by means of the last-observation-carried-forward method. To provide estimates of expected change from baseline and treatment effect, we used a mixed-effect model repeated measure (MMRM) approach that was based on log-transformed data. Log transformation was predicted to approximately normalize data on the basis of experience from phase 3 studies of relapsing multiple sclerosis and from assessment of the distributions for timed 25-foot walk and the volume of lesions on T_2-weighted images within the blinded ORATORIO data. For brain volume, P values and estimates were based on MMRM analysis of percent change from baseline. Ranked ANCOVA and MMRM analyses were adjusted for baseline values, geographic region, and age.

RESULTS

PATIENTS

From March 3, 2011, through December 27, 2012, a total of 732 patients underwent randomization (intention-to-treat population); 488 were assigned to receive ocrelizumab and 244 to receive placebo. Baseline demographic and disease characteristics were balanced between the trial groups (Table 1). A total of 402 patients (82%) who were assigned to ocrelizumab and 174 (71%) assigned to placebo reached 120 weeks in the trial. A total of 549 patients (387 [79%] assigned to ocrelizumab and 162 [66%] assigned to placebo) were still receiving the blinded trial agent when the prespecified number of primary-outcome events was attained to designate the clinical cutoff date for the double-blind phase of the trial (Fig. S2 in the Supplementary Appendix). The median trial duration was 2.9 years in the ocrelizumab group and 2.8 years in the placebo group.

EFFICACY

Clinical End Points

The percentage of patients with 12-week confirmed disability progression (primary end point) was 32.9% with ocrelizumab versus 39.3% with placebo (hazard ratio, 0.76; 95% confidence interval [CI], 0.59 to 0.98; relative risk reduction, 24%; P=0.03) (Table 2 and Fig. 1A). The percentage of patients with 24-week confirmed disability progression (first secondary end point in the analysis hierarchy) was 29.6% with ocrelizumab and 35.7% with placebo (hazard ratio, 0.75; 95% CI, 0.58 to 0.98; relative risk reduction, 25%; P=0.04) (Table 2 and Fig. 1B). The mean change from baseline to week 120 in performance on the timed 25-foot walk (second secondary end point) was 38.9% with ocrelizumab versus 55.1% with placebo (relative reduction with ocrelizumab, 29.3%; 95% CI, –1.6 to 51.5; P=0.04) (Table 2). There was no significant between-group difference in the change in the SF-36 Physical Component Summary score from baseline to week 120 (fifth secondary end point; adjusted mean change, –0.7 with ocrelizumab and –1.1 with placebo; P=0.60) (Table 2).

The results of sensitivity analyses of the primary end point and first secondary end point that evaluated the influence of physician-reported clinical relapses or protocol-defined relapses on disability-progression data were consistent with the primary results, as were the results of sensitivity analyses that used alternative imputation approaches for patients with initial disability progression (Tables S4 and S10 in the Supplementary Appendix). The result of a subgroup analysis of efficacy end points in patients with and without

Table 1. Baseline Demographic and Disease Characteristics (Intention-to-Treat Population).*

Characteristic	Ocrelizumab (N = 488)	Placebo (N = 244)
Age — yr		
Mean	44.7±7.9	44.4±8.3
Median (range)	46.0 (20–56)	46.0 (18–56)
Female sex — no. (%)	237 (48.6)	124 (50.8)
Time since onset of MS symptoms — yr†		
Mean	6.7±4.0	6.1±3.6
Median (range)	6.0 (1.1–32.9)	5.5 (0.9–23.8)
Time since diagnosis of PPMS — yr‡		
Mean	2.9±3.2	2.8±3.3
Median (range)	1.6 (0.1–16.8)	1.3 (0.1–23.8)
No previous use of disease-modifying therapy — no. (%)§	433 (88.7)	214 (87.7)
Score on EDSS¶		
Mean	4.7±1.2	4.7±1.2
Median (range)	4.5 (2.5–7.0)	4.5 (2.5–6.5)
Gadolinium-enhancing lesions on T_1-weighted images — no./total no. (%)		
Yes‖	133/484 (27.5)	60/243 (24.7)
No	351/484 (72.5)	183/243 (75.3)
No. of lesions on T_2-weighted images**		
Mean	48.7±38.2	48.2±39.3
Median (range)	42.0 (0–249.0)	43.0 (0–208.0)
Total volume of lesions on T_2-weighted images — cm^3**		
Mean	12.7±15.1	10.9±13.0
Median (range)	7.3 (0–90.3)	6.2 (0–81.1)
Normalized brain volume — cm^3††		
Mean	1462.9±84.0	1469.9±88.7
Median (range)	1462.2 (1214.3–1711.1)	1464.5 (1216.3–1701.7)

* Plus–minus values are means ±SD. Patients were stratified according to geographic region (United States vs. rest of the world) and age (≤45 vs. >45 years). MS denotes multiple sclerosis, and PPMS primary progressive MS.
† Data were not available for 14 patients in the ocrelizumab group and 7 patients in the placebo group.
‡ Data were not available for 2 patients in the ocrelizumab group and 1 patient in the placebo group.
§ Shown are data for patients with no use of disease-modifying therapy in the 2 years before trial entry.
¶ Scores on the Expanded Disability Status Scale (EDSS) range from 0 to 10, with higher scores indicating greater disability. Data were not available for 1 patient in the ocrelizumab group.
‖ A breakdown of the categorical numbers of gadolinium-enhancing lesions on T_1-weighted images is provided in Table S7 in the Supplementary Appendix.
** Data were not available for 2 patients in the ocrelizumab group and 1 patient in the placebo group.
†† The analysis was performed with the use of SIENA/X.[22] Data were not available for 6 patients in the ocrelizumab group and 1 patient in the placebo group.

gadolinium-enhancing lesions on T_1-weighted images at baseline was directionally consistent with the findings in the overall trial population. The trial was not powered to show between-group differences among these subgroups (Table S5 in the Supplementary Appendix). Whether signs of active inflammation at baseline might represent a potential treatment-effect–modifying factor remains to be further elucidated.

Several exploratory end points with direct bearing on the primary analysis were analyzed (Table S3 and Figs. S3 and S4 in the Supplementary

Table 2. Primary and Secondary End Points, According to Hierarchical Order in the Statistical Analysis (Intention-to-Treat Population).*

End Point	Ocrelizumab (N = 488)	Placebo (N = 244)	Hazard Ratio or Relative Difference (95% CI)†	P Value
Confirmed disability progression for ≥12 wk: primary end point — no./total no. (%)‡	160/487 (32.9)	96/244 (39.3)	0.76 (0.59 to 0.98)	0.03
Secondary clinical end points				
Confirmed disability progression for ≥24 wk — no./total no. (%)‡	144/487 (29.6)	87/244 (35.7)	0.75 (0.58 to 0.98)	0.04
Mean percent change in performance on timed 25-ft walk from baseline to wk 120§	38.9	55.1	29.3 (−1.6 to 51.5)¶	0.04
Secondary MRI end points				
Adjusted geometric mean percent change in total volume of lesions on T_2-weighted images from baseline to wk 120 (95% CI)‖	−3.37 (−4.99 to −1.72)	7.43 (4.97 to 9.94)	0.90 (0.88 to 0.92)	<0.001
Mean percent change in brain volume from wk 24 to 120 (95% CI)**	−0.90 (−1.00 to −0.80)	−1.09 (−1.24 to −0.95)	17.5 (3.2 to 29.3)¶	0.02
Adjusted mean change in SF-36 Physical Component Summary score from baseline to wk 120: secondary patient-reported end point (95% CI)††	−0.73 (−1.66 to 0.19)	−1.11 (−2.39 to 0.18)	0.38 (−1.05 to 1.80)	0.60

* CI denotes confidence interval.
† Values other than hazard ratios or relative differences are indicated in the corresponding footnotes for those end points.
‡ One patient in the ocrelizumab group was excluded from the analysis owing to missing data on the EDSS score at baseline. The P value was calculated with the use of the log-rank test.
§ The P value was calculated with the use of a ranked analysis of covariance (ANCOVA) at the 120-week visit, with adjustment for the baseline performance on the timed 25-ft walk, geographic region, and age and with missing values imputed by last observation carried forward. Point estimates and 95% confidence intervals were calculated with the use of a mixed-effect model repeated measure (MMRM) analysis of log-transformed data, with adjustment for the baseline performance on the timed 25-ft walk, geographic region, and age.
¶ Shown is the percent reduction relative to placebo.
‖ The between-group difference for this end point is the ratio of the adjusted geometric mean for ocrelizumab versus placebo. The P value was calculated with the use of a ranked ANCOVA at the 120-week visit, with adjustment for baseline volume of lesions on T_2-weighted images, geographic region, and age and with missing values imputed by last observation carried forward. Point estimates and 95% confidence intervals were calculated with the use of an MMRM analysis of log-transformed data, with adjustment for baseline volume of lesions on T_2-weighted images, geographic region, and age.
** The P value was calculated with the use of an MMRM approach at the 120-week visit, with adjustment for week 24 brain volume, geographic region, and age.
†† The between-group difference for this end point is the numerical difference in adjusted means. Scores on the Physical Component Summary of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), version 2, range from 0 to 100, with higher scores indicating better physical-health–related quality of life. The P value was calculated with the use of an MMRM approach at the 120-week visit, with adjustment for baseline SF-36 Physical Component Summary score, geographic region, and age.

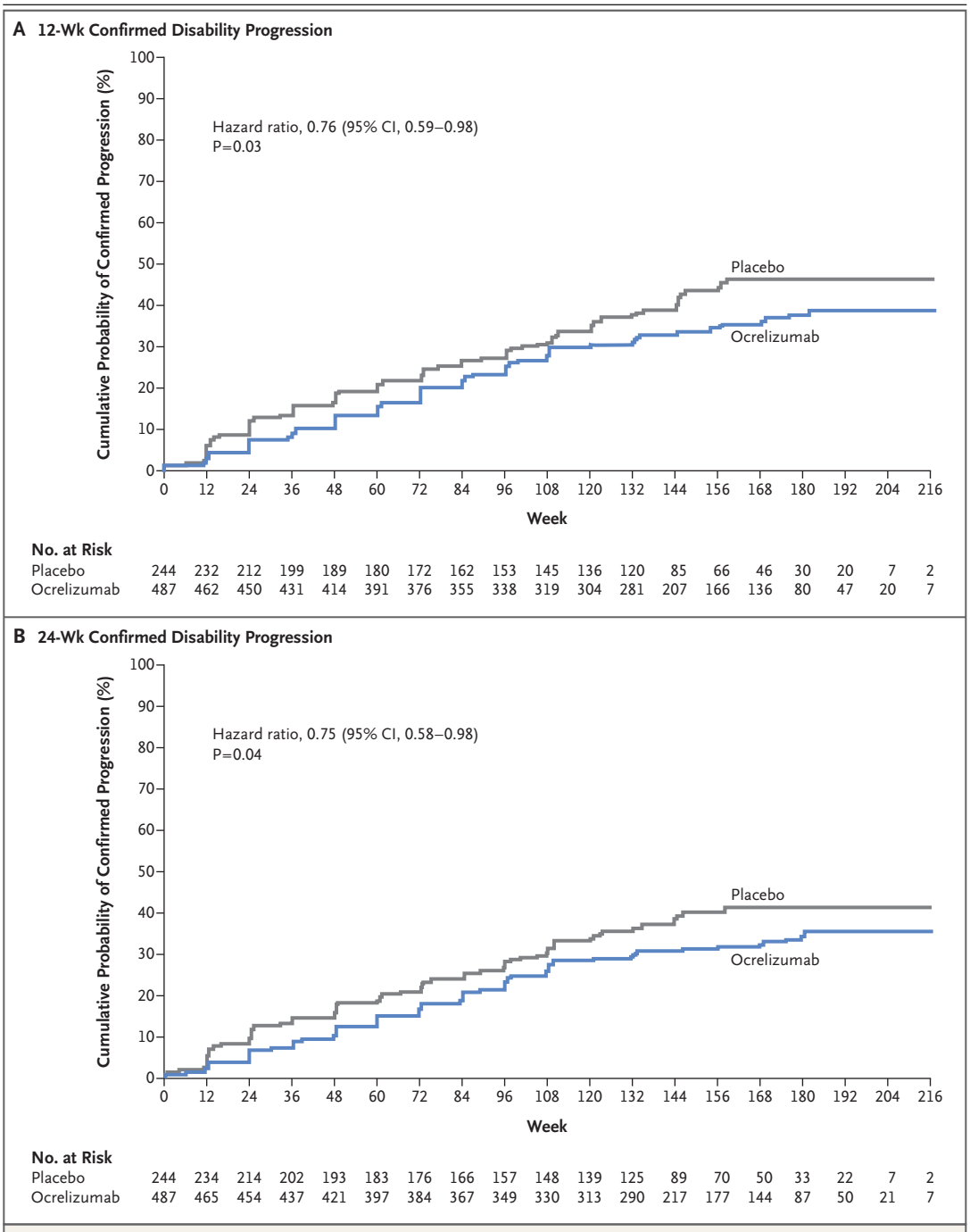

Figure 1. Primary and Key Secondary Clinical Outcomes (Intention-to-Treat Population).

Panel A (primary end point) and Panel B (first secondary end point) show the cumulative probability of clinical disability progression (as defined by an increase in the score on the Expanded Disability Status Scale) that was confirmed after at least 12 weeks and at least 24 weeks, respectively, in time-to-event analyses. P values were calculated with the use of the log-rank test.

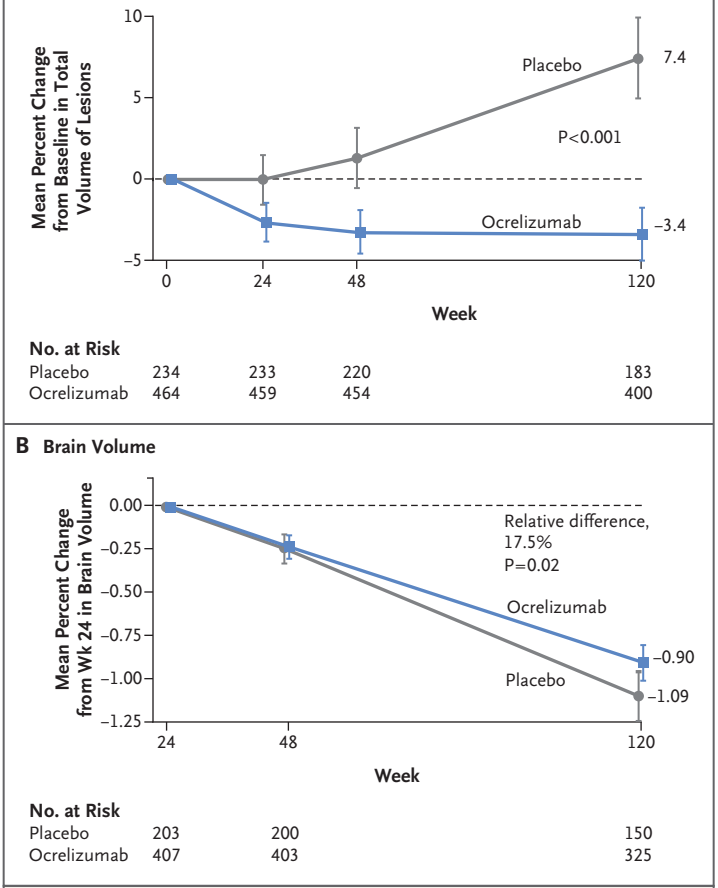

Figure 2. MRI End Points (Intention-to-Treat Population).

Panel A shows the percent change in the total volume of brain lesions on T_2-weighted MRI from baseline to week 120 (third secondary end point). The P value was calculated with the use of a ranked analysis of covariance. Panel B shows the percent change on MRI scans in brain volume from week 24 to week 120 (fourth secondary end point). The P value was calculated with the use of a mixed-effect model repeated measure (MMRM) approach. I bars indicate 95% confidence intervals.

Appendix). The prespecified exploratory analysis of 12-week and 24-week confirmed composite disability progression and its components significantly favored ocrelizumab.

Brain MRI End Points

The total volume of hyperintense lesions on T_2-weighted images from baseline to week 120 (third secondary end point) decreased with ocrelizumab and increased with placebo (mean percent change, –3.4 vs. 7.4; P<0.001) (Table 2 and Fig. 2A). The adjusted mean percent change in brain volume from week 24 to week 120 (fourth secondary end point) was lower with ocrelizumab than with placebo (–0.90 vs. –1.09, P=0.02) (Table 2 and Fig. 2B). The adjusted mean number of new or enlarging hyperintense lesions on T_2-weighted images from baseline to week 120 (exploratory end point) was lower with ocrelizumab than with placebo (0.31 vs. 3.88, P<0.001) (Table S3 in the Supplementary Appendix).

SAFETY

Adverse Events

A total of 725 patients (486 in the ocrelizumab group and 239 in the placebo group) received at least one dose of a trial agent and were included in the safety analysis population. The percentage of patients who had at least one adverse event was 95.1% with ocrelizumab and 90.0% with placebo. Serious adverse events were reported among 20.4% of those who received ocrelizumab and 22.2% of those who received placebo (Table 3). Overall, the rates of adverse events per 100 patient-years did not differ significantly between the ocrelizumab group and the placebo group (260.5 [95% CI, 252.2 to 269.1] and 267.0 [95% CI, 254.7 to 279.8], respectively), with no increase over time or with subsequent doses. Adverse events that led to discontinuation of the trial agent occurred among 4.1% of patients who received ocrelizumab and 3.3% of patients who received placebo.

The most frequently reported adverse event among ocrelizumab-treated patients was infusion-related reaction: 39.9% of those who received ocrelizumab reported at least one infusion-related reaction as compared with 25.5% of those who received placebo. More patients in the ocrelizumab group than in the placebo group had adverse events leading to modification of the infusion rate or interruption of infusions (9.7% vs. 5.0%). Two patients (0.4%) withdrew from ocrelizumab treatment because of infusion-related reactions. Infusion-related reactions decreased in both rate and severity with subsequent administration; none were fatal or life-threatening (Fig. S5 in the Supplementary Appendix). The percentage of patients who reported upper respiratory tract infections was higher in the ocrelizumab group than in the placebo group (10.9% vs. 5.9%). Overall, five deaths were reported: four (0.8%) in the ocrelizumab group owing to pulmonary embolism, pneumonia, pancreatic carcinoma, and aspiration pneumonia and one (0.4%) in the placebo group owing to a road-traffic accident.

Table 3. Adverse Events (Safety Population).*

Event	Ocrelizumab (N=486)	Placebo (N=239)
Any adverse event — no. of patients (%)†	462 (95.1)	215 (90.0)
Adverse event leading to discontinuation of trial agent — no. of patients (%)	20 (4.1)	8 (3.3)
Death — no. of patients (%)‡	4 (0.8)	1 (0.4)
Infusion-related reactions		
≥1 Reaction — no. of patients (%)	194 (39.9)	61 (25.5)
Total no. of reactions	485	145
Grade of reaction — no. of patients (%)		
1: mild	129 (26.5)	38 (15.9)
2: moderate	59 (12.1)	19 (7.9)
3: severe	6 (1.2)	4 (1.7)
4: life-threatening	0	0
5: death	0	0
Any serious adverse event — no. of patients (%)	99 (20.4)	53 (22.2)
Serious infections — no. of patients (%)	30 (6.2)	14 (5.9)
Neoplasms — no. of patients (%)§	11 (2.3)	2 (0.8)
Breast cancer	4 (0.8)¶	0
Basal-cell carcinoma	3 (0.6)	1 (0.4)
Adenocarcinoma of the cervix	0	1 (0.4)
Anaplastic large-cell lymphoma	1 (0.2)	0
Endometrial adenocarcinoma	1 (0.2)	0
Malignant fibrous histiocytoma	1 (0.2)	0
Metastatic pancreatic carcinoma	1 (0.2)	0

* Adverse events were coded according to the preferred terms in the *Medical Dictionary for Regulatory Activities*, version 18.0. This table contains data collected up until the end of the double-blind controlled treatment period as of the clinical cutoff date (July 24, 2015). For an up-to-date list of adverse events (including serious adverse events) that is based on information available as of January 20, 2016, see Table S8 in the Supplementary Appendix. Four patients who were assigned to the placebo group received a single dose of ocrelizumab treatment; these patients were included in the ocrelizumab group in the safety analysis.

† For the adverse events reported by at least 10% of the patients in either group, see Table S9 in the Supplementary Appendix.

‡ Deaths occurring during the trial were due to a road-traffic accident in the placebo group and pulmonary embolism, pneumonia, pancreatic carcinoma, and aspiration pneumonia in the ocrelizumab group.

§ For an up-to-date list of all additional neoplasms recorded in the latest extended safety follow-up analysis of all exposure up until June 30, 2016 (including respective open-label extension phases) of the OPERA I trial (ClinicalTrials.gov number, NCT01247324), OPERA II trial (NCT01412333), ORATORIO trial (NCT01194570), and phase 2 studies (NCT00676715) of ocrelizumab in multiple sclerosis, see Table S6 in the Supplementary Appendix.

¶ Two events were coded as invasive ductal breast carcinoma and one each as breast cancer and invasive breast carcinoma.

Infections

The percentage of patients reporting any infection was 71.4% in the ocrelizumab group and 69.9% in the placebo group. The most common infections (i.e., with a frequency of ≥10% in one of the trial groups) were nasopharyngitis (22.6% with ocrelizumab and 27.2% with placebo), urinary tract infection (19.8% with ocrelizumab and 22.6% with placebo), influenza (11.5% with ocrelizumab and 8.8% with placebo), and upper respiratory tract infection (as noted above). The percentage of patients with serious infections according to system organ class was similar in the two groups (6.2% with ocrelizumab and 5.9% with placebo) and changed little with the use of a broader definition of serious infections, which included

nonserious infections that were treated with an intravenous antiinfective agent (7.6% with ocrelizumab and 8.8% with placebo). Among all herpesvirus-related infections (4.7% with ocrelizumab and 3.3% with placebo), oral herpes was more common among patients who received ocrelizumab than among those who received placebo (2.3% vs. 0.4%); all cases were mild to moderate — that is, corresponding to grade 1 or 2 according to the Common Terminology Criteria for Adverse Events. (Additional details are provided in the Safety section in the Supplementary Appendix.)

Laboratory Assessments

After the first infusion of ocrelizumab, levels of CD4-expressing T cells remained stable throughout the treatment period, whereas there was an initial mean decrease of 2 to 6% from baseline in peripheral-blood counts of CD3+ or CD8+ cells, apparent at week 2. An additional 6% decrease was observed from week 2 to week 120 for CD8-expressing cells. This finding differed from a stable course of CD8-expressing cells in the placebo group, in which an initial 4 to 5% mean increase in CD3+ or CD4+ cells was observed at week 2 and was maintained thereafter. There was no effect of ocrelizumab treatment on natural killer (CD16+ or CD56+) cells, with a mean increase of approximately 3% in each group from baseline to week 120. (Additional details on immunoglobulin levels and antidrug antibodies are provided in the Safety section in the Supplementary Appendix.)

Neoplasms

Over the controlled treatment period, neoplasms were reported in 11 of 486 patients (2.3%) in the ocrelizumab group (breast cancer in 4 patients, basal-cell carcinoma in 3, and endometrial adenocarcinoma, anaplastic large-cell lymphoma [mainly T cells], malignant fibrous histiocytoma, and pancreatic carcinoma in 1 each) and in 2 of 239 patients (0.8%) in the placebo group (cervical adenocarcinoma in situ and basal-cell carcinoma in 1 each). Between the clinical cutoff date (July 24, 2015) and June 30, 2016, two additional cases of neoplasm (one case each of basal-cell skin carcinoma and squamous-cell carcinoma) were detected during the open-label extension phase in which all patients received ocrelizumab. As of June 30, 2016, the overall incidence of a first neoplasm among patients with multiple sclerosis who were treated with ocrelizumab across all studies (ClinicalTrials.gov numbers, NCT01247324, NCT01412333, NCT00676715, and NCT01194570) was 0.40 per 100 patient-years of exposure (6467 patient-years of exposure) as compared with 0.20 per 100 patient-years for pooled comparator groups (interferon beta-1a or placebo, 2053 patient-years of exposure) (Table S6 in the Supplementary Appendix).

DISCUSSION

In this trial, the results favored ocrelizumab over placebo with respect to the risk of confirmed disability progression at 12 weeks, the primary end point, and the first four of five secondary end points: 24-week confirmed disability progression, ambulation speed as assessed by the timed 25-foot walk, change in the total volume of brain lesions on T_2-weighted images, and change in brain volume. However, there was no significant between-group difference in the physical component of the SF-36. The magnitude of the effect of ocrelizumab on clinical end points was similar when we compared the results for 12-week and 24-week confirmed disability progression.

Infusion-related reactions were more frequent among patients who received ocrelizumab than those who received placebo. Such reactions were most commonly observed with the first infusion, decreased with subsequent doses, and were treated with premedication and infusion adjustments.[23]

The imbalance in observed neoplasms in the ocrelizumab group as compared with the placebo group warrants ongoing evaluation in the context of the epidemiology of neoplasms in the population with multiple sclerosis and long-term experience with ocrelizumab and other anti-CD20 treatments.[24-26] No cases of progressive multifocal leukoencephalopathy (PML) have been reported so far with ocrelizumab across all clinical studies of the drug, but further assessment is required to characterize the risk of uncommon adverse events, including PML.

Safety will continue to be assessed throughout the open-label extension phase. These data, along with those from other studies involving patients with relapsing and primary progressive multiple

sclerosis, may help to determine the long-term benefit–risk profile of ocrelizumab. As in all clinical trials, caution should prevail in the expansion of the interpretation of trial results beyond the limits of the studied population and duration of the trial.

Pathological studies suggest that progressive-onset multiple sclerosis is part of a spectrum of overlapping phenotypes.[27] The efficacy of ocrelizumab in our trial indicates that B cells contribute to the pathogenesis of primary progressive multiple sclerosis and that B-cell–mediated inflammation has a direct or indirect role in neurodegeneration.[28,29]

Supported by F. Hoffmann–La Roche.

Dr. Montalban reports receiving consulting fees, lecture fees, and travel support from Actelion Pharmaceuticals, Almirall, Bayer, Biogen Idec, Celgene, Genzyme, Merck, Novartis Pharmaceuticals, Roche, Sanofi Genzyme, and Teva Pharmaceuticals; Dr. Hauser, receiving fees for serving on advisory boards from Bionure, Symbiotix, Annexon Biosciences, and Molecular Stethoscope, serving as a board of trustees member for Neurona Therapeutics, and receiving travel support from Roche; Dr. Kappos, receiving royalties from Neurostatus Systems and grant support to his institution from Actelion Pharmaceuticals, Bayer HealthCare, Biogen Idec, CSL Behring, df-mp, Genzyme, Merck, Mitsubishi Pharma, Novartis Pharmaceuticals, Pfizer, Receptos, Roche, Sanofi-Aventis, Santhera Pharmaceuticals, Teva Pharmaceuticals, UCB Pharma, the Roche Research Foundations, Alkermes, Almirall, Excemed, GeNeuro, Vianex, and Allergan; Dr. Arnold, receiving personal fees from Acorda Therapeutics, Biogen Idec, MedImmune, Mitsubishi Pharma, Novartis Pharmaceuticals, Receptos, Roche, and Sanofi-Aventis, receiving grant support from Biogen Idec and Novartis Pharmaceuticals, and holding equity in NeuroRx; Dr. Bar-Or, receiving fees for lectures and serving on advisory boards from Amplimmune, Atara Biotherapeutics, Biogen Idec, Genentech, GlaxoSmithKline, Guthy-Jackson/GGF, MedImmune, Merck/EMD Serono, Mitsubishi Pharma, Novartis Pharmaceuticals, Ono Pharma, Receptos, Roche, Sanofi Genzyme, and Teva Pharmaceuticals and research support from Novartis Pharmaceuticals and Sanofi Genzyme; Dr. Comi, receiving consulting and lecture fees from Teva Pharmaceuticals, Sanofi, Genzyme, Merck, Biogen Idec, Excemed, Almirall, Receptos, Forward Pharma, Celgene, Bayer, and the Serono Symposia International Foundation; Dr. de Seze, receiving fees for serving on advisory boards from Roche, Biogen Idec, Merck, Teva Pharmaceuticals, Almirall, CSL Behring, and Novartis Pharmaceuticals, consulting fees from Teva Pharmaceuticals and Novartis Pharmaceuticals, and grant support from Biogen Idec, Merck, Teva Pharmaceuticals, CSL Behring, and Novartis Pharmaceuticals; Dr. Giovannoni, receiving consulting fees from AbbVie, Biogen Idec, Canbex Therapeutics, GW Pharmaceuticals, Merck Serono, Novartis Pharmaceuticals, Roche, Synthon, Teva Pharmaceuticals, and Vertex Pharmaceuticals and grant support from Biogen Idec, Canbex Therapeutics, Merck Serono, Novartis Pharmaceuticals, and Teva Pharmaceuticals; Dr. Hartung, receiving fees for serving on steering committees from Biogen Idec, GeNeuro, Sanofi Genzyme, Merck, Novartis Pharmaceuticals, Octapharma, Opexa Therapeutics, Teva Pharmaceuticals, MedImmune, Bayer HealthCare, Forward Pharma, and Roche, fees for serving on advisory boards from Biogen Idec, Sanofi Genzyme, Merck, Novartis Pharmaceuticals, Octapharma, Opexa Therapeutics, Teva Pharmaceuticals, and Roche, and lecture fees from Biogen Idec, Sanofi Genzyme, Merck, Novartis Pharmaceuticals, Octapharma, Opexa Therapeutics, Teva Pharmaceuticals, MedImmune, and Roche; Dr. Hemmer, receiving fees for board membership from Roche, Novartis Pharmaceuticals, and Bayer, consulting fees and travel support from Roche, Biogen Idec, Novartis Pharmaceuticals, Merck, Bayer, and Teva Pharmaceuticals, and grant support from Chugai, Roche, and MedImmune; Dr. Lublin, fees for serving on advisory boards from Bayer Healthcare, Biogen Idec, EMD Serono, Novartis Pharmaceuticals, Teva Pharmaceuticals, Actelion Pharmaceuticals, Sanofi Genzyme, Acorda Therapeutics, Questcor/Mallinckrodt, Roche/Genentech, Celgene, MedImmune, Osmotica Pharmaceutical, XenoPort, Receptos, Forward Pharma, BBB Technologies, Akros, TG Therapeutics, AbbVie, MedDay, and Atara Biotherapeutics and grant support from Biogen Idec, Novartis Pharmaceuticals, Teva Neuroscience, Sanofi Genzyme, Celgene, and Transparency Life Sciences; Dr. Rammohan, receiving fees for serving on advisory boards from Biogen Idec, EMD Serono, Genzyme, Novartis Pharmaceuticals, Teva Pharmaceuticals, and Acorda Therapeutics and grant support from Novartis Pharmaceuticals; Dr. Selmaj, receiving fees for serving on advisory boards from Biogen Idec, Novartis Pharmaceuticals, Roche, Teva Pharmaceuticals, Receptos, Synthon, and Genzyme and consulting fees from Bayer; Dr. Traboulsee, receiving fees for serving on an advisory board from Biogen Idec, consulting fees from Chugai and Teva Pharmaceuticals, lecture fees from Sanofi Genzyme, and grant support from Biogen Idec, Sanofi Genzyme, Chugai, and Teva Pharmaceuticals; Dr. Sauter, being an employee of Roche; Dr. Masterman, being an employee of Genentech; Dr. Fontoura, being an employee of and holding stock in Roche; Dr. Belachew, being an employee of Roche; Dr. Garren, being an employee of and holding stock in Roche; Dr. Mairon, being an employee of Roche; Dr. Chin, being an employee of and holding stock in Genentech, being a former employee of and holding stock in Novartis Pharmaceuticals, and being a named inventor on pending patents related to methods for treating progressive multiple sclerosis (US20100158903; WO2010033587; held by Genentech); and Dr. Wolinsky, receiving fees for serving on data and safety monitoring boards from Sanofi, Teva Pharmaceuticals, and Novartis Pharmaceuticals, fees for serving on advisory boards from Teva Pharmaceuticals, Genzyme, AbbVie, Forward Pharma, Novartis Pharmaceuticals, Bayer HealthCare, and Celgene, fees for serving on a steering committee from Roche, consulting fees from Teva Pharmaceuticals, Genzyme, Actelion Pharmaceuticals, AbbVie, XenoPort, EMD Serono, Alkermes, Forward Pharma, Novartis Pharmaceuticals, Takeda Pharmaceuticals, Roche, Genentech, and Strategic Consultants, lecture fees from Teva Pharmaceuticals, Genzyme, WebMD, and AcademicCME, grant support from Sanofi-Aventis and Genzyme, and royalties from Millipore (formerly Chemicon International). No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients for making this trial possible; the members of the independent data and safety monitoring committee: Stephen C. Reingold, Magnhild Sandberg-Wollheim, Scott Evans, Henry F. McFarland, Israel Steiner, Thomas Dörner, and Frederik Barkhof; Natalie Nkwor of Articulate Science for writing assistance and editorial assistance with earlier versions of the manuscript; Gurpreet Deol-Bhullar for scientific contribution to the trial; and Alexander Kulla, Michele Libonati, and Mercedes McClean for critical review and technical advice during the preparation of this manuscript.

APPENDIX

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