Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial

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Summary

Background B lymphocytes are implicated in the pathogenesis of multiple sclerosis. We aimed to assess efficacy and safety of two dose regimens of the humanised anti-CD20 monoclonal antibody ocrelizumab in patients with relapsing-remitting multiple sclerosis.

Methods We did a multicentre, randomised, parallel, double-blind, placebo-controlled study involving 79 centres in 20 countries. Patients aged 18–55 years with relapsing-remitting multiple sclerosis were randomly assigned (1:1:1:1) via an interactive voice response system to receive either placebo, low-dose (600 mg) or high-dose (2000 mg) ocrelizumab in two doses on days 1 and 15, or intramuscular interferon beta-1a (30 μg) once a week. The randomisation list was not disclosed to the study centres, monitors, project statisticians or to the project team at Roche. All groups were double blinded to group assignment, except the interferon beta-1a group who were rater masked. At week 24, patients in the initial placebo, 600 mg ocrelizumab, and interferon beta-1a groups received ocrelizumab 600 mg; the 2000 mg group received 1000 mg. Our primary endpoint was the total number of gadolinium-enhancing lesions (GEL) and T1-weighted MRI at weeks 12, 16, 20, and 24. Analyses were done on an intention-to-treat basis. This trial is registered with ClinicalTrials.gov, number NCT00676715.

Findings 218 (99%) of the 220 randomised patients received at least one dose of ocrelizumab, 204 (93%) completed 24 weeks of the study and 196 (89%) completed 48 weeks. In the intention-to-treat population of 218 patients, at week 24, the number of gadolinium-enhancing lesions was 89% (95% CI 68–97; p<0·0001) lower in the 600 mg ocrelizumab group than in the placebo group, and 96% (89–99; p<0·0001) lower in the 2000 mg group. In exploratory analyses, both 600 mg and 2000 mg ocrelizumab groups were better than interferon beta-1a for GEL reduction. We noted serious adverse events in two of 54 (4%; 95% CI 3·0–4·4) patients in the placebo group, one of 55 (2%; 1·3–2·3) in the 600 mg ocrelizumab group, three of 55 (5%; 4·6–6·3) in the 2000 mg group, and two of 54 (4%; 3·0–4·4) in the interferon beta-1a group.

Interpretation The similarly pronounced effects of B-cell depletion with both ocrelizumab doses on MRI and relapse-related outcomes support a role for B-cells in disease pathogenesis and warrant further assessment in large, long-term trials.

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Introduction

Inflammation in multiple sclerosis was previously thought to be mainly mediated by proinflammatory CD4 T cells (Th1, ThIL-17).[1] However, B cells might also contribute to multiple sclerosis through antibody-dependent and antibody-independent mechanisms. B cells might differentiate into plasma cells and produce CNS-directed autoantibodies, triggering cellular and complement-dependent cytotoxic effects.[2] These cells can also function as antigen-presenting cells and thereby modulate priming of effector T cells.[3] Secretion of proinflammatory and anti-inflammatory cytokines by B cells is a function that seems to be abnormal in patients with multiple sclerosis.[4–6] Production of cytokines and chemokines by B cells could also contribute to formation of ectopic lymphoid-like structures, resulting in CNS-compartmentalised presentation of autoantigens and further immune activation.[7,8] B cells could also be the reservoir for Epstein-Barr virus, Therefore, targeting of these cells might disrupt processes in multiple sclerosis pathogenesis.

Studies of rituximab—a chimeric monoclonal antibody against CD20—have shown that B-cell depletion is of clinical benefit as treatment for some lymphoma types, chronic lymphocytic leukaemia,[9] and rheumatoid arthritis[10–12] and as a potential treatment for multiple sclerosis.[13] Ocrelizumab is a recombinant humanised antibody designed to selectively target CD20 B cells. Compared with rituximab, ocrelizumab is associated with increased antibody-dependent cell-mediated cytotoxic effects, and reduced complement-dependent cytotoxic effects in vitro.[14,15] By increasing antibody-dependent cell-mediated cytotoxic effects, ocrelizumab might modulate tissue-dependent mechanisms of pathogenic response more effectively than does rituximab. As a humanised molecule, ocrelizumab is expected to be less immunogenic with repeated infusions and might thus have a more

We did this phase-2, placebo-controlled trial to assess efficacy and safety of two dose regimens of ocrelizumab in patients with relapsing-remitting multiple sclerosis. We also compared ocrelizumab with once a week interferon beta-1a (avonex) as open-label treatment.

Methods

Patients

We recruited patients from 79 centres in 20 countries, and did an international multicentre, randomised, parallel, double-blind, placebo-controlled, dose-finding study with ocrelizumab. 58 patients were from centres in North America, 120 from centres in east-central Europe and Asia, 34 from centres in western Europe, and eight from centres in Latin America. Eligible patients were aged 18–55 years with a diagnosis of relapsing-remitting multiple sclerosis,[16] had had two or more documented relapses within 3 years before screening, at least one of which occurred within the past year, had expanded disability status scale (EDSS)[17] score of 1–6 points at baseline, and evidence of previous multiple sclerosis inflammatory disease activity with six T2 lesions or more per MRI, or two relapses in the year before screening.

Key exclusion criteria were secondary or primary progressive multiple sclerosis; disease duration more than 15 years in patients with an EDSS of 2 or less; known history or presence of other neurological or systemic autoimmune disorders; treatment with rituximab or lymphocyte-depleting therapies; use of lymphocyte trafficking blockers within previous 24 weeks; use of β interferons, glatiramer acetate, intravenous immunoglobulin, plasmapheresis, and immunosuppresive treatments within previous 12 weeks, use of systemic glucocorticoids within previous 4 weeks; or intolerance to interferon beta-1a. After a screening period of up to 4 weeks, eligible patients began treatment consisting of four treatment cycles of 24 weeks. This period was followed by a treatment-free follow-up and observation period of about 172 weeks from randomisation, dependent on the time taken for B-cell repletion.

For more on **neurological assessment criteria** see http://www.neurostatus.net

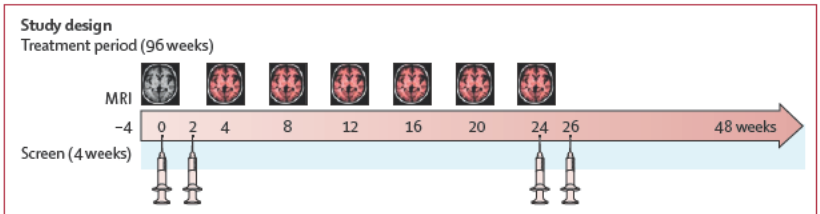
Institutional Review Board approval was obtained at each trial site. We did the study in accordance with International Conference on Harmonization Good Clinical Practice guidelines, and with the Declaration of Helsinki. Patients provided written informed consent before participation.

Procedures

Our primary objective was to investigate the effect of ocrelizumab on the total number of gadolinium-enhancing T1 lesions observed on brain MRI scans for weeks 12, 16, 20, and 24 versus placebo. A fourth study group with interferon beta-1a was included as an active, open label, rater-masked control (figure 1). Key secondary endpoints included the annualised protocol-defined relapse rate; proportion of relapse-free patients; total number of gadolinium-enhancing T1 lesions (all data-points from 4–24 weeks); total number of new gadolinium-enhancing T1 lesions; change in total volume of T2 lesions from baseline to week 24; safety and tolerability of two dose regimens of ocrelizumab versus placebo and interferon beta-1a at week 24; and safety of ocrelizumab therapy up to 96 weeks. Here we present the results of the 24-week placebo and interferon beta-1a controlled phase, and results of the second cycle for another 24 weeks, in which patients in comparator groups were switched to ocrelizumab.

Every study site had two investigators: the treating investigator and the examining investigator. The treating investigator had access to safety and efficacy data, and made all treatment decisions on the basis of patients' clinical responses and laboratory findings. A trained and certified examining investigator, who had no access to other study or patient-related information, did a full neurological examination, including assessment of walking capacity, and assigned the functional systems and EDSS.

We obtained brain MRI (proton density and T2-weighted images, T1-weighted images before and after gadolinium enhancement) scans at baseline and thereafter at intervals of 4 weeks to week 24, and centrally reviewed and analysed the scans with no clinical information to ensure they were masked. Patients were assessed for relapse by the treating investigator at each visit throughout the study and, if necessary, at unscheduled visits. We designated protocol-defined relapses as the occurrence of new or worsening neurological symptoms attributable to multiple sclerosis, and immediately preceded by a stable or improving neurological state of at least 30 days. Symptoms had to



Screening	Randomisation	Treatment period			
28 days	Group	First cycle		Second cycle	
		Day 1	Day 15	Day 1	Day 15
	Placebo	Intravenous placebo	Intravenous placebo	Intravenous ocrelizumab 300 mg	Intravenous ocrelizumab 300 mg
	Ocrelizumab 600 mg	Intravenous ocrelizumab 300 mg	Intravenous ocrelizumab 300 mg	Intravenous ocrelizumab 600 mg	Intravenous placebo
	Ocrelizumab 2000 mg	Intravenous ocrelizumab 1000 mg	Intravenous ocrelizumab 1000 mg	Intravenous ocrelizumab 1000 mg	Intravenous placebo
	Interferon beta-1a	Intramuscular avonex 30 µg every week		Intravenous ocrelizumab 300 mg	Intravenous ocrelizumab 300 mg

Figure 1: Study design and treatment protocol

objective neurological worsening consistent with an increase of at least half a step on the EDSS, or two points on one, or one point on two or more of the functional systems scores. The examining investigator assessed disability progression (measured by EDSS) at screening and every 12 weeks throughout the study. We defined such progression as an increase of 1 point or more from baseline EDSS score confirmed at the next scheduled examination 3 months after initial screening. In addition to routine laboratory tests, we examined CD19 B-cell counts, immunoglobulin concentrations (total immunoglobulin, IgG, IgM, and IgA), ocrelizumab concentrations, and human antihuman antibodies against ocrelizumab.

The 600 mg ocrelizumab group had a dual infusion of 300 mg for the first treatment cycle (days 1 and 15), and then infusions of 600 mg for the subsequent treatment cycles (weeks 24, 48, and 72). The 2000 mg group had a dual infusion of 1000 mg (days 1 and 15) for the first treatment cycle, and then an infusion of 1000 mg for the subsequent treatment cycles. Patients in the placebo group received placebo on days 1 and 15 of the first treatment cycle. The interferon beta-1a group received intramuscular interferon beta-1a once a week for the first 24 weeks. The placebo and interferon beta-1a groups were offered ocrelizumab 600 mg for the second, third, and fourth treatment cycles (figure 1). Safety was assessed at weeks 2, 4, 8, 12, 16, 20, 24, and 48 with regular neurological and physical examinations, vital signs, electrocardiograph, and the occurrence of adverse events. By week 24, six patients withdrew for safety reasons. One patient in the 2000 mg ocrelizumab group died of systemic inflammatory response syndrome of undetermined origin. We did JC virus testing for early detection and follow-up in case of suspected progressive multifocal leukoencephalopathy every 12 weeks. We assessed clinical relapses in the efficacy and safety analyses and recorded every relapse as an adverse event. Although defined retrospectively, we also recorded progression of relapsing-remitting multiple sclerosis to secondary progressive multiple sclerosis as an adverse event. All study MRIs underwent safety review by the site radiologist to identify any new clinically relevant abnormal MRI findings that were not consistent with the diagnosis of multiple sclerosis, with particular attention to the possibility of progressive multifocal leukoencephalopathy, and to provide a report of the MRI to the treating investigator.

To reduce potential infusion-related reactions, 30 min before the start of each infusion, patients in the ocrelizumab or placebo groups received intravenous methylprednisolone 100 mg. Patients in the interferon

	Placebo (n=54)	Ocrelizumab 600 mg (n=55)	Ocrelizumab 2000 mg (n=55)	Interferon beta-1a (n=54)
Age (years)	38·0 (8·8)	35·6 (8·5)	38·5 (8·7)	38·1 (9·3)
Sex				
Female	36 (67%)	35 (64%)	38 (69%)	32 (59%)
Race				
White*	52 (96%)	51 (93%)	53 (96%)	53 (98%)
Disease duration (years)				
Since onset of MS symptoms	4·8 (0·6–26·2)	6·5 (0·5–20·5)	7·7 (0·25–28·0)	5·3 (0·8–35·2)
Since MS diagnosis	2·7 (0·1–19·2)	3·6 (0·1–16·5)	4·4 (0·1–19·2)	3·3 (0·1–20·2)
Relapses in past 3 years				
1	4 (7%)	1 (2%)	1 (2%)	0 (··)
2	26 (48%)	28 (51%)	30 (55%)	30 (56%)
3	15 (28%)	16 (29%)	14 (25%)	21 (39%)
≥4	9 (17%)	10 (18%)	10 (18%)	3 (6%)
Baseline EDSS	3·2 (1·4); 3·0 (1·0–6·0)	3·5 (1·5); 3·5 (1·0–6·0)	3·4 (1·3); 3·5 (1·0–6·0)	3·1 (1·5); 2·8 (1·0–6·0)
Volume of T2 lesions at baseline (mm³)	8951 (9776·3); 4765 (47–39 920)	13 973 (19 930·2); 6688 (11–93778)	13 178 (14 271·4); 7125 (203–59 432)	13 209 (17 206·5); 8247 (24–102 912)
Gadolinium-enhancing T1 lesions	1·6 (4·05); 0 (0–25); IQR (0–1)	3·9 (9·88); 1 (0–46); IQR (0–3)	2·2 (6·33); 0 (0–37); IQR (0–1)	2·3 (5·26); 0 (0–24); IQR (0–1)
Total gadolinium-enhancing T1 lesion count (%)				
0	26 (55%)	25 (49%)	29 (55%)	33 (66%)
1	11 (23%)	6 (12%)	12 (23%)	7 (14%)
2	2 (4%)	6 (12%)	4 (8%)	2 (4%)
3	2 (4%)	6 (12%)	2 (4%)	0 (··)
≥4	6 (13%)	8 (16%)	6 (11%)	8 (16%)
No previous immunomodulatory treatment	38 (70%)	26 (47%)	27 (49%)	37 (69%)

Data are mean (SD), n (%), or median (min–max), unless otherwise stated. MS=multiple sclerosis. EDSS=expanded disability status scale. *The study was done in mainly white individuals; others were mostly black (six individuals) and Chinese (two).

beta-1a group received this concomitant treatment at the corresponding time at days 1 and 15 during the first treatment cycle. We recommended preinfusion treatment with an oral analgesic or antipyretic (eg, acetaminophen), and an oral antihistaminine (eg, diphenhydramine).

Randomisation and masking

A randomisation list was generated by an independent group within Roche. This list was provided to an interactive voice response system, which then randomised patients (1:1:1:1) to one of the four treatment groups stratified by geographical region (figure 1). The list was not disclosed to the study centres, monitors, project statisticians, or to the project team at Roche and Genentech. All individuals directly involved in this study remain blinded to the dose of ocrelizumab. Project statisticians remained blinded until data lock and statistical analysis at week 24. We masked treatment assignment for patients in the placebo and both ocrelizumab groups throughout the study. In the interferon beta-1a group, only the raters were masked to allocation; therefore comparisons of the other groups with this group on the primary and secondary outcomes were exploratory.

Statistical analysis

On the basis of results from the rituximab proof-of-concept study,[13] we estimated a sample size of 35 patients per group was needed to provide 80% power with a two-sided significance level of 0·05 to detect a difference in the total number of gadolinium-enhancing T1 lesions between each ocrelizumab group versus placebo with the Wilcoxon rank-sum test. To allow for drop-outs, we planned for up to 50 patients to be randomly assigned to each treatment group. Because screening was faster than expected, once all sites were started, we allowed a maximum of 220 patients to be randomly assigned to avoid exclusion of scheduled patients. We did no interim analysis. Analysis was by intention to treat. We applied the van Elteren test, stratified by geographical region and presence of baseline gadolinium-enhancing lesions (absent or present), to compare each ocrelizumab group

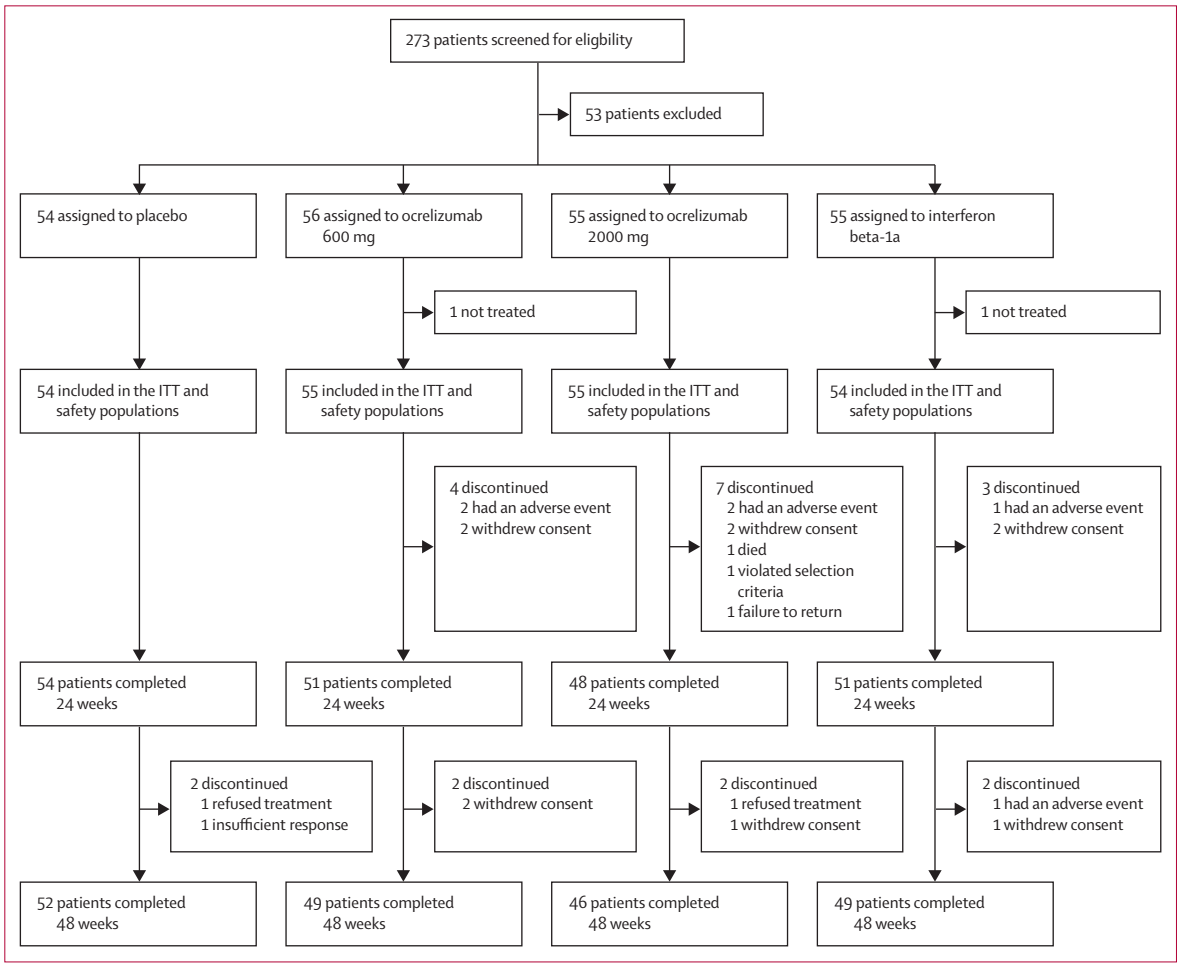


Figure 2: Trial profile

with placebo for the primary endpoint. We replaced missing values for gadolinium-enhancing T1 lesions with the average number of lesions on available scans from that patient obtained during the first 24 weeks of treatment, excluding MRIs that were done after early termination from the treatment period. We did similar analyses for other lesion-count endpoints.

We analysed annualised relapse rates with Poisson regression, offsetting for exposure time in years, and adjusting for geographical region. No imputation was

	Placebo (n=54)	Ocrelizumab 600 mg (n=55)	Ocrelizumab 2000 mg (n=55)	Interferon beta-1a (n=54)
MRI				
Total number of galodinium-enhancing T1 lesions over weeks 12, 16, 20, and 24*				
n (%)	54 (100%)	51 (93%)	52 (95%)	52 (96%)
Mean (SD)	5·5 (12·5)	0·6 (1·5)	0·2 (0·7)	6·9 (16·0)
Median (min–max)	1·6 (0–79)	0·0 (0–7)	0·0 (0–3)	1·0 (0–78)
95% CI	0·8–2·6	..	..	0·0–2·0
p value (ocrelizumab vs placebo)†	..	<0·0001	<0·0001	..
p value (ocrelizumab vs interferon beta-1a)†	..	<0·0001	<0·0001	..
Total number of galodinium-enhancing T1 lesions over weeks 12, 16, 20, and 24 by category* (%)				
0	19 (35%)	39 (77%)	43 (82·7%)	25 (48%)
1	6 (11%)	2 (4%)	6 (11·5%)	5 (10%)
2	7 (13%)	6 (12%)	1 (1·9%)	5 (10%)
3	3 (6%)	0	2 (3·8%)	0
≥4	19 (35%)	4 (8%)	0	17 (33%)
p value vs placebo‡	..	<0·0001	<0·0001	0·4182
Total number of new galodinium-enhancing lesions over weeks 4, 8, 12, 16, 20, and 24*				
Mean (SD)	6·6 (14·2)	0·8 (2·0)	0·8 (2·2)	7·2 (16·3)
Median (min–max)	2·2 (0–93)	0·0 (0–11)	0·0 (0–14)	1·0 (0–95)
95% CI	1·0–4·0	0·0–0·0	0·0–0·0	0·0–2·0
p value vs placebo†	..	<0·0001	<0·0001	0·9
Change in volume of T2 lesion from baseline to week 24				
n (%)	47 (87%)	47 (85%)	46 (84%)	48 (89%)
Mean (SD)	−114·0 (1400·8)	−841·4 (2702·2)	−578·1 (2109·2)	996·7 (4418·1)
Median (min–max)	5·2 (-5689·2 to 2504·9)	−65·8 (-16298·6 to 1520·3)	−17·1 (-7301·2 to 5212·5)	0·0 (-6713·8 to 25459·4)
95% CI	−42·1 to 179·2	−179·1 to −5·3	−679·5 to −60·5	−121·2 to 292·4
p value vs placebo§	..	0·2	0·2	0·5
Total number of new or enlarging T2 lesions at week 24				
n (%)	54 (100%)	51 (94%)	52 (96%)	52 (96%)
Mean (SD)	1·4 (3·3)	0·0 (0·1)	0·0 (0·1)	1·8 (5·2)
p value vs placebo§	..	<0·0001	<0·0001	0·3
Relapses				
Total number of patients with relapses by week 24 (%)¶	16 (30%)	3 (5%)	4 (7%)	9 (17%)
Annualised relapse rate by week 24	0·64	0·13	0·17	0·36
95% CI	0·43–0·94	0·53–0·29	0·05–0·35	0·22–0·60
p value vs placebo‖	0·07	0·0005	0·0014	0·07
p value vs interferon beta-1a‖	..	0·03	0·09	..
Proportion relapse-free at week 24 (%)	41 (76%)	48 (87%)	45 (82%)	42 (78%)
95% CI**	64·5–87·3	78·5–96·1	71·6–92·0	66·7–88·9
Relative risk compared with placebo (95% CI)	..	0·53 (0·23–1·22)	0·76 (0·36–1·57)	0·92 (0·46–1·84)
Total number of relapses between week 24 and week 48 (%)¶	4 (7·4%)	2 (3·9%)	6 (10·6%)	3 (5·9%)
Annualised relapse rate between weeks 24 and 48 (95% CI)‖	0·16 (0·09–0·30)	0·09 (0·04–0·20)	0·28 (0·17–0·47)	0·14 (0·07–0·28)
Proportion relapse-free from weeks 24 to 48 (%)	49 (91%)	47 (92%)	42 (89%)	46 (90%)
95% CI**	83·0–98·5	84·8–99·5	80·5–98·2	82·0–98·4

Data are mean (SD), n (%), and median (IQR), unless otherwise stated. *Missing value at a timepoint is imputed with the average of available after baseline observations and before week 24. †Van Elteren test stratified by geographical region and presence of baseline gadolinium-enhancing lesions (absent or present). ‡Fischer's Exact test. §Van Elteren test stratified by geographical region. ¶Observational values. ||Poisson regression, offsetting for exposure time in years and adjusting for geographical region. **We counted patients who discontinued early without having a relapse as having a relapse.

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