

ORIGINAL ARTICLE

Oral Fingolimod (FTY720) for Relapsing Multiple Sclerosis

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ABSTRACT

BACKGROUND

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N Engl J Med 2006;355:1124-40.
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Fingolimod (FTY720) is a new oral immunomodulating agent under evaluation for the treatment of relapsing multiple sclerosis.

METHODS

We randomly assigned 281 patients to receive oral fingolimod, at a dose of 1.25 mg or 5.0 mg, or a placebo once daily, and we followed these patients for 6 months with magnetic resonance imaging (MRI) and clinical evaluations (core study, months 0 to 6). The primary end point was the total number of gadolinium-enhanced lesions recorded on T₁-weighted MRI at monthly intervals for 6 months. In an extension study in which the investigators and patients remained unaware of the dose assignments (months 7 to 12), patients who received placebo underwent randomization again to one of the fingolimod doses.

RESULTS

A total of 255 patients completed the core study. The median total number of gadolinium-enhanced lesions on MRI was lower with 1.25 mg of fingolimod (1 lesion, $P < 0.001$) and 5.0 mg of fingolimod (3 lesions, $P = 0.006$) than with placebo (5 lesions). The annualized relapse rate was 0.77 in the placebo group, as compared with 0.35 in the group given 1.25 mg of fingolimod ($P = 0.009$) and 0.36 in the group given 5.0 mg of fingolimod ($P = 0.01$). For the 227 patients who completed the extension study, the number of gadolinium-enhanced lesions and relapse rates remained low in the groups that received continuous fingolimod, and both measures decreased in patients who switched from placebo to fingolimod. Adverse events included nasopharyngitis, dyspnea, headache, diarrhea, and nausea. Clinically asymptomatic elevations of alanine aminotransferase levels were more frequent with fingolimod (10 to 12%, vs. 1% in the placebo group). One case of the posterior reversible encephalopathy syndrome occurred in the 5.0-mg group. Fingolimod was also associated with an initial reduction in the heart rate and a modest decrease in the forced expiratory volume in 1 second.

CONCLUSIONS

In this proof-of-concept study, fingolimod reduced the number of lesions detected on MRI and clinical disease activity in patients with multiple sclerosis. Evaluation in larger, longer-term studies is warranted. (Clinicaltrials.gov numbers, NCT00333138 [core study] and NCT00235430 [extension].)

MULTIPLE SCLEROSIS IS THE MOST COMMON nontraumatic cause of neurologic disability in young adults.^{1,2} It is generally believed to be an autoimmune condition in which autoreactive T cells attack myelin sheaths,³ leading to demyelination and axonal damage.⁴ Currently approved immunomodulating treatments for multiple sclerosis (interferon beta and glatiramer acetate)⁵⁻⁸ reduce relapse rates by about 30%.⁹ Both these drugs are administered either subcutaneously or intramuscularly, and interferons are associated with systemic reactions in more than 60% of patients,¹⁰ with implications for adherence to treatment.¹¹

Fingolimod (FTY720, Novartis Pharma) is an oral sphingosine-1-phosphate receptor modulator. After rapid phosphorylation, fingolimod-P acts as a superagonist of the sphingosine-1-phosphate-1 receptor on thymocytes and lymphocytes and induces aberrant internalization of this receptor, thereby depriving these cells of a signal necessary to egress from secondary lymphoid tissues. The majority of circulating lymphocytes are thus sequestered in lymph nodes, reducing peripheral lymphocyte counts and the recirculation of lymphocytes to the central nervous system.¹²⁻¹⁵ Lymphocytes in secondary lymphoid organs and those remaining in blood continue to be functional. In laboratory animals, fingolimod does not impair memory T-cell activation or expansion in response to systemic viral infection.¹⁶ In animal models of multiple sclerosis, fingolimod prevents the onset of disease and reduces established neurologic deficits.^{12,17,18}

We conducted a double-blind, placebo-controlled, proof-of-concept clinical study to evaluate the efficacy and safety of fingolimod for the treatment of relapsing multiple sclerosis.

METHODS

The steering-committee members and the sponsors designed the study. The authors had access to all data, participated in the analysis and interpretation of data, and were members of the publication committee. The academic authors vouch for the completeness and veracity of the data and analyses.

PATIENTS

Eligible patients were 18 to 60 years of age and had a diagnosis of relapsing multiple sclerosis¹⁹

and at least one of the following: two or more documented relapses during the previous 2 years, one or more documented relapses in the year before enrollment, and one or more gadolinium-enhanced lesions detected on magnetic resonance imaging (MRI) at screening. Additional eligibility criteria included a score of 0 to 6 on the Expanded Disability Status Scale (EDSS, on which scores range from 0 to 10, with higher scores indicating a greater degree of disability)²⁰ and neurologically stable condition, with no evidence of relapse for at least 30 days before screening and during the screening and baseline phases. Exclusion criteria were use of corticosteroids (within the previous 30 days), immunomodulatory therapy (within the previous 3 months), or immunosuppressive treatment (e.g., azathioprine or methotrexate within 6 months, cyclophosphamide within 12 months, or mitoxantrone or cladribine within 24 months); a history of cardiac conditions that might increase the risk of a decrease in heart rate; a white-cell count of less than 3500 per cubic millimeter; and a lymphocyte count of less than 800 per cubic millimeter.

The study adhered to the International Conference on Harmonization Guidelines for Good Clinical Practice²¹ and was conducted in accordance with the Declaration of Helsinki.²² An independent external data and safety monitoring board evaluated adverse events and other safety data as well as clinical and MRI efficacy data. All patients gave written informed consent.

STUDY DESIGN AND RANDOMIZATION

The study included a 6-month double-blind core study (months 0 to 6) and a 6-month extension study during which the investigators and patients were unaware of treatment assignments (months 7 to 12).

In the core study, patients were randomly assigned, in a 1:1:1 ratio, to 1.25 mg of fingolimod, 5.0 mg of fingolimod, or a matching placebo once daily; all drugs were given as capsules. Randomization was stratified according to disease course (relapsing–remitting or secondary progressive) with the use of a centralized automated system that provided randomized packages of the study drug to each center. The medication was prepackaged on the basis of a block size of 3 (1.25 mg, 5.0 mg, and placebo); this information was not disclosed to investigators and monitors.

After the core study, patients could continue

in the extension study. Participating patients received a new set of medication and were unaware of the treatment assignment; those who had received active treatment in the core study continued with the same dose, and those who had received placebo were randomly assigned to receive 1.25 or 5.0 mg of fingolimod.

Study visits took place at screening, at baseline, on days 1 and 7, and then monthly for 6 months. In the extension study, visits took place on day 1 and at months 9 and 12. MRI of the brain was performed at baseline, monthly for 6 months, and at month 12, with the use of standard, predefined acquisition settings. T₁-weighted, T₂-weighted, and proton and density sequences were obtained before the administration of gadolinium. T₁-weighted sequences were also obtained after the administration of gadolinium. Vital signs were obtained at each visit, and laboratory and hematologic measures were obtained at baseline, day 1, and months 1, 3, 6, 9, and 12. Electrocardiograms were obtained at baseline, on days 1 and 7, and at months 1, 3, 6, and 12, and 24-hour Holter electrocardiographic monitoring was performed at selected sites at baseline, day 1, and month 3. Pulmonary-function tests, which included the forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), and carbon monoxide diffusion capacity, were performed at screening and months 6 and 12. These tests were introduced by means of a protocol amendment and thus were performed in a subgroup of patients. Neurologic evaluations were performed at baseline and every 3 months thereafter with the use of the EDSS and the Multiple Sclerosis Functional Composite (MSFC, data not shown). Relapses were confirmed by the treating physician on the basis of an examination by the EDSS rater who was not otherwise involved in patient care. When warranted, relapses were managed by the treating physician according to a standardized scheme, with up to 1000 mg of methylprednisolone per day given intravenously for 3 to 5 days.

STUDY END POINTS AND PROCEDURES

As previously suggested for phase 2 proof-of-concept trials in relapsing multiple sclerosis,^{23,24} the primary efficacy end point of the study was the total number of gadolinium-enhanced lesions per patient recorded on T₁-weighted MRI at monthly intervals for 6 months. Secondary

MRI variables included the total volume of gadolinium-enhanced lesions per patient, the proportion of patients with gadolinium-enhanced lesions, the total number of new lesions per patient on T₂-weighted images, changes in lesion volume on T₂-weighted images, and brain volume from baseline to month 6.

Clinical end points included the number of patients remaining free of relapse, the annualized relapse rate, and the time to the first relapse. Confirmed relapse was defined as the occurrence of new symptoms or worsening of previously stable or improving symptoms and signs not associated with fever, lasting more than 24 hours and accompanied by an increase of at least half a point in the EDSS score or 1 point in the score for at least one of the functional systems (excluding the bowel and bladder and mental systems). Neurologic deterioration that was classified by the treating physician as a relapse but that did not fulfill these criteria was documented as an unconfirmed relapse. In the core study, we performed exploratory assessments of disability by comparing scores on the MSFC and EDSS at baseline with scores at month 6. For the extension study, values at baseline and month 6 were compared with values at month 12.

MRI scans were assessed for quality and compliance at the MS-MRI Evaluation Center in Basel without the evaluators' knowledge of treatment assignments or clinical results. Lesion volumes were measured with the use of an interactive digital-analysis program.²⁵ Brain volume was measured with the Structural Image Evaluation Using Normalisation of Atrophy (SIENA) program.²⁶ Neurologic assessments were performed by specially trained,²⁷ independent neurologists who were unaware of the treatment assignments, were not involved in the everyday care of the patients, and had no access to their medical records.

Adverse events were assessed and reported at each visit (scheduled and unscheduled) by the treating physicians. Laboratory evaluations were undertaken at a central laboratory. Laboratory values that might have revealed the treatment assignment (e.g., lymphocyte counts) were not disclosed to treating physicians unless they exceeded prespecified safety limits. In cases of clinical adverse events or notable laboratory abnormalities, the dose of study medication was reduced or withheld at the discretion of the treating neurologist.

Rechallenge after improvement was performed at the discretion of the treating neurologist.

STATISTICAL ANALYSIS

Statistical power and sample size were calculated on the basis of data from the Sylvia Lawry Centre for Multiple Sclerosis Research,²⁸ with a nonparametric bootstrap method²⁹ with a two-sided Wilcoxon rank-sum test and a 5% significance level. For a study with 80 patients per group, we estimated that the study would have a power of 78% if the number of post-baseline lesions on MRI was reduced by 50% in the fingolimod groups, as compared with the placebo group. Assuming that we would be able to evaluate data for more than 90% of patients, the enrollment of 72 patients with data that could be evaluated in each group would be sufficient to detect a significant treatment effect of 50% with a power of 75%.

As prespecified, MRI analyses were primarily performed in a population of patients who underwent randomization and who completed 6 months of treatment, had no major protocol violations, and for whom MRI scans were available at baseline and on three or more visits. Use of a per-protocol-like population for MRI analyses is appropriate for a proof-of-concept study. The intention-to-treat population comprised all patients who were randomly assigned to receive at least one dose of study medication and had at least one post-baseline MRI. MRI analyses were repeated for the intention-to-treat population to assess the sensitivity of the results with the population with data that could be evaluated. Clinical outcomes were evaluated in the intention-to-treat population. Safety analyses were undertaken for patients who were randomly assigned to receive at least one dose of study drug and completed at least one safety assessment. Adverse events were analyzed by means of Fisher's exact test.

MRI end points were compared among the groups with the use of nonparametric Wilcoxon rank-sum tests. The probability of a first confirmed relapse was calculated by the Kaplan-Meier method, with between-group comparisons made with the log-rank test. Proportions of patients who were free of relapse at month 6 on the basis of Kaplan-Meier estimates were compared with the use of the z-test. We used a Poisson regression model to compare annualized relapse rates. Baseline characteristics were assessed with Fisher's

exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. P values are based on two-sided tests. No interim analysis was performed. No adjustments were made for multiple comparisons.

When scans were missing, patients discontinued treatment, or MRI was performed within 14 days after corticosteroid treatment and the results were therefore considered invalid, the median of number and volume of gadolinium-enhanced lesions and the number of new lesions on monthly T₂-weighted scans available post-baseline was imputed. Each patient therefore had six complete scans, and the totals were compared among treatments with a nonparametric Wilcoxon rank-sum test. Additional analyses were performed with data from the intention-to-treat population and actual lesion counts only (i.e., without imputed data). These analyses included Wilcoxon rank-sum tests for between-group comparisons of the average number of lesions per scan and per patient and generalized estimation equations³⁰ with the use of longitudinal data and adjustment for baseline covariates. The Wilcoxon signed-rank test was used for within-group comparisons of MRI outcomes in the extension study.

RESULTS

PATIENTS

Patients were recruited by investigators from 32 centers in 10 European countries and Canada from May 2003 to April 2004. In the 12-month extension study, the assessment for the last patient was completed in April 2005.

Figure 1 shows the numbers of patients who were randomly assigned to the three study groups and who completed treatment. Baseline characteristics were similar among the three groups (Table 1).

MRI RESULTS IN THE CORE STUDY

The total cumulative numbers of lesions per patient on post-baseline, monthly gadolinium-enhanced, T₁-weighted MRI scans were lower in both fingolimod groups than in the placebo group (P<0.001 for the 1.25-mg dose and P=0.006 for the 5.0-mg dose) (Table 2).

At month 6, the proportion of patients who were free of gadolinium-enhanced lesions was greater in both fingolimod groups than in the

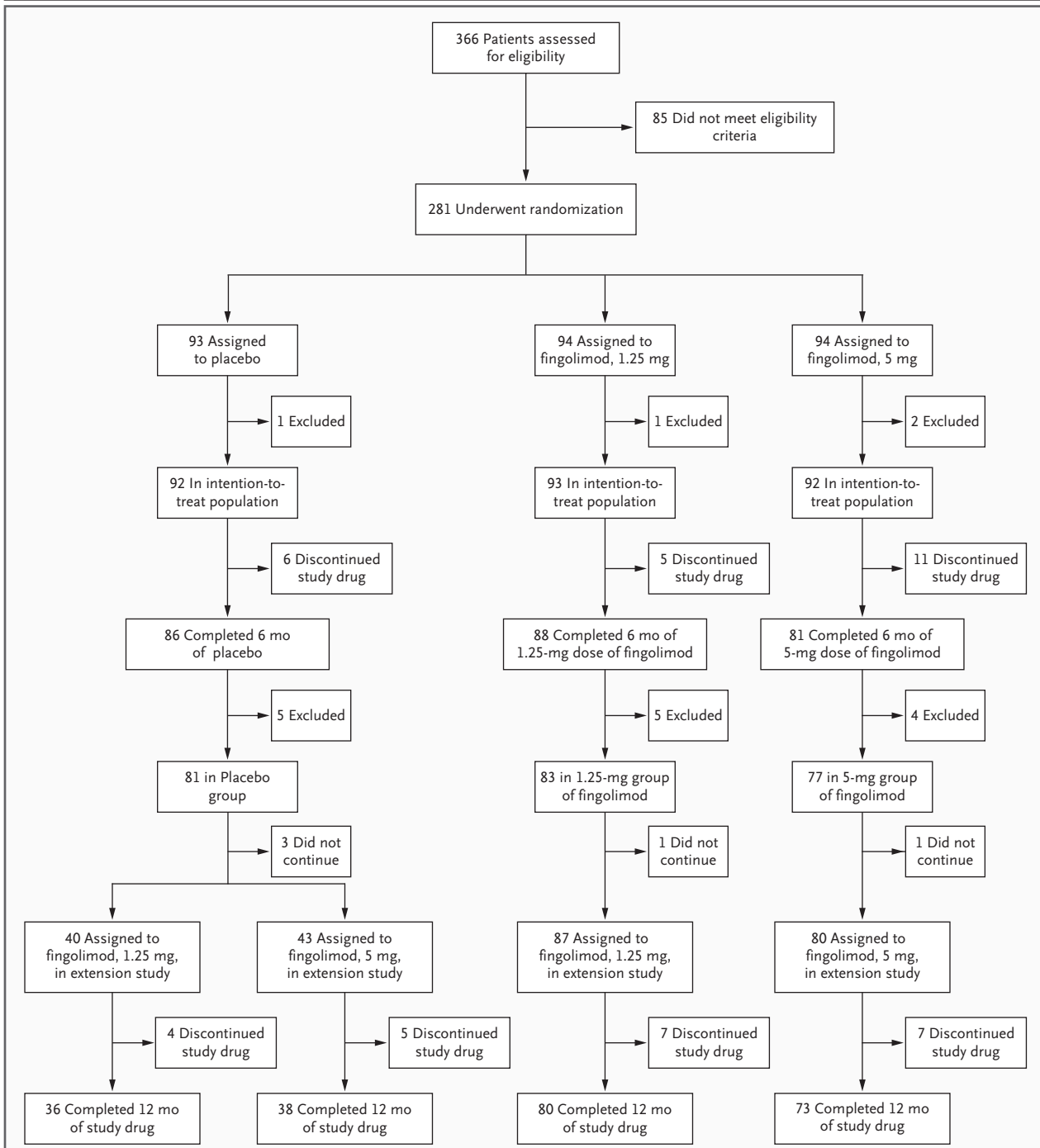


Figure 1. Numbers of Patients Who Underwent Randomization and Who Completed Treatment.

Four patients did not have one or more scans available after baseline and therefore were not included in the intention-to-treat analysis. The most common reasons for premature discontinuation were adverse events and withdrawal of consent. In addition to the patients who prematurely discontinued study medication, 14 patients were excluded from the population that could be evaluated because baseline and three post-baseline MRI scans were not available or the protocol was violated. These 14 patients completed the core study and were eligible to enter the extension phase.

Table 1. Baseline Characteristics of the Patients.

Characteristic	Placebo (N=92)	Fingolimod, 1.25 mg (N=93)	Fingolimod, 5.0 mg (N=92)
Intention-to-treat population			
Age — yr			
Mean	37.1	38.0	38.3
Range	19–56	19–60	18–59
Age — no. (%)			
≤30 yr	24 (26)	23 (25)	26 (28)
31–40 yr	33 (36)	38 (41)	26 (28)
41–50 yr	30 (33)	21 (23)	24 (26)
>50 yr	5 (5)	11 (12)	16 (17)
Male sex — no. (%)	31 (34)	23 (25)	27 (29)
Interval since first symptoms — yr			
Mean	8.4	8.6	9.5
Range	0.2–28.2	0.3–50.2	0.5–42.2
Course of disease — no. (%)			
Relapsing–remitting	83 (90)	83 (89)	80 (87)
Secondary progressive	9 (10)	10 (11)	12 (13)
No. of relapses in previous yr			
Mean	1.2	1.3	1.3
Range	0–5	0–5	0–4
No. of relapses in previous 2 yr			
Mean	1.8	1.9	1.9
Range	0–6	0–8	0–8
Time since most recent relapse — mo			
Mean	9.2	7.3	6.3
Median (range)	6.3 (2–95)	6.1 (1–26)	5.3 (0–26)
EDSS score*			
Mean	2.6	2.7	2.5
Median (range)	2.0 (0.0–6.5)	2.5 (0.0–6.0)	2.0 (0.0–6.0)
Primary MRI analysis population†			
No. of T ₁ -weighted, gadolinium-enhanced lesions at baseline			
Mean	2.8	3.4	2.8
Median (range)	1.0 (0–47)	0 (0–72)	1.0 (0–54)
Patients with T ₁ -weighted, gadolinium-enhanced lesions at baseline — no. (%)	41 (51)	39 (47)	44 (57)
Volume of lesions at baseline — mm ³			
T ₁ -weighted, gadolinium-enhanced			
Mean	417	232	268
Median (range)	16 (0–6341)	0 (0–3106)	32 (0–5002)
T ₂ -weighted			
Mean	8805	10,219	8722
Median (range)	5499 (123–62,218)	4237 (293–104,504)	4750 (349–70,218)

* Scores range from 0 to 10; higher scores indicate a greater degree of disability. Scores were available for 91 patients in the placebo group, 93 in the 1.25-mg group, and 91 in the 5.0-mg group.

† Data were available for 81 patients in the placebo group, 83 in the 1.25-mg group, and 77 in the 5-mg group.

placebo group ($P < 0.001$ for both comparisons), with a separation between the curves becoming evident from 2 months onward (Fig. 2A). With the exception of the change in brain volume from baseline, all secondary MRI end points differed significantly between the fingolimod groups and the placebo, in each case favoring treatment with fingolimod (Table 2).

In the population with data that could be evaluated, only 1% of scans were missing or invalid (i.e., with the use of imputed values), as compared with 6% in the intention-to-treat population. When sensitivity analyses of data with and without imputation were performed for the

intention-to-treat population, all MRI findings were similar to those in the population with data that could be evaluated and all significant differences were maintained.

CLINICAL OUTCOMES IN THE CORE STUDY

Although the study was not powered to detect a treatment effect on the relapse end points, significant improvements over placebo were observed in the fingolimod groups, including a relative reduction in the annualized relapse rate (by 53% in the 5.0-mg group and by 55% in the 1.25-mg group) (Table 2). In addition, the estimated time to a first relapse was significantly prolonged in

Table 2. MRI and Clinical End Points at 6 Months in the Core Study.

End Point	Placebo	Fingolimod, 1.25 mg	Fingolimod, 5.0 mg	P Value	
				1.25 mg vs. Placebo	5.0 mg vs. Placebo
Primary MRI analysis population					
No. evaluated	81	83	77		
Total cumulative no. of gadolinium-enhanced lesions					
Mean \pm SD	14.8 \pm 22.5	8.4 \pm 23.7	5.7 \pm 11.6	<0.001	0.006
Median (range)	5 (0–114)	1 (0–182)	3 (0–91)		
No. of gadolinium-enhanced lesions at 6 mo					
Mean \pm SD	2.21 \pm 4.3	1.29 \pm 5.8	0.27 \pm 0.7	<0.001	<0.001
Median (range)	1 (0–26)	0 (0–48)	0 (0–3)		
Patients free of gadolinium-enhanced lesions at 6 mo — no. (%)	38 (47)	64 (77)	63 (82)	<0.001	<0.001
Total cumulative volume of gadolinium-enhanced lesions — mm ³					
Mean \pm SD	1418 \pm 2349	715 \pm 1658	530 \pm 1260	0.002	0.009
Median (range)	335 (0 to 10,975)	69 (0 to 9058)	137 (0 to 7806)		
Volume of gadolinium-enhanced lesions at 6 mo — mm ³					
Mean \pm SD	242 \pm 641	79 \pm 294	34 \pm 98	<0.001	<0.001
Median (range)	17.2 (0 to 4232)	0 (0 to 1772)	0 (0 to 504)		
Total cumulative no. of new T ₂ lesions					
Mean \pm SD	6.4 \pm 9.2	3.0 \pm 8.6	1.9 \pm 2.6	<0.001	<0.001
Median (range)	3 (0 to 45)	0 (0 to 66)	1 (0 to 13)		
Change in T ₂ volume from baseline — mm ³					
Mean	+129	–113	–627	0.10	<0.001
Median (range)	–16 (–5056 to 6801)	–97 (–4916 to 4050)	–220 (–10,041 to 5734)		
Change in brain volume from baseline					
Mean	–0.31	–0.22	–0.40	0.77	0.20
Median (range)	–0.15 (–3.2 to 1.5)	–0.29 (–1.3 to 1.4)	–0.34 (–1.9 to 1.0)		

the fingolimod groups (Fig. 2B). Inclusion of unconfirmed relapses yielded similar results. There were no significant differences in disability (EDSS scores) at 12 months between the fingolimod groups and the placebo group (Table 2).

EXTENSION STUDY

Of the 255 patients who completed the core study, 250 (98%) continued in the extension study (Fig. 1). A total of 227 of these 250 patients (91%) completed the 6-month extension study, for a total of 12 months in the overall study.

At month 12, the number of gadolinium-enhanced lesions remained low in the two groups of patients who received continuous treatment with fingolimod, whereas the number decreased significantly among the patients who switched

from placebo to fingolimod (Table 3). Other MRI variables consistently showed that fingolimod continued to have a marked effect on inflammatory activity, as reflected by MRI findings (Table 3). At month 12, more than 80% of patients who received fingolimod were free of gadolinium-enhanced lesions.

Among patients who switched from placebo to fingolimod, the annualized relapse rate was lower during the period of treatment with fingolimod (Table 3). The relapse rates in the groups of patients who received continuous fingolimod remained low during months 7 to 12, with overall 12-month relapse rates of 0.31 and 0.29 for the 1.25-mg dose and the 5.0-mg dose, respectively.

In both groups of patients who received continuous fingolimod, 79% were free of relapse at

Table 2. (Continued.)

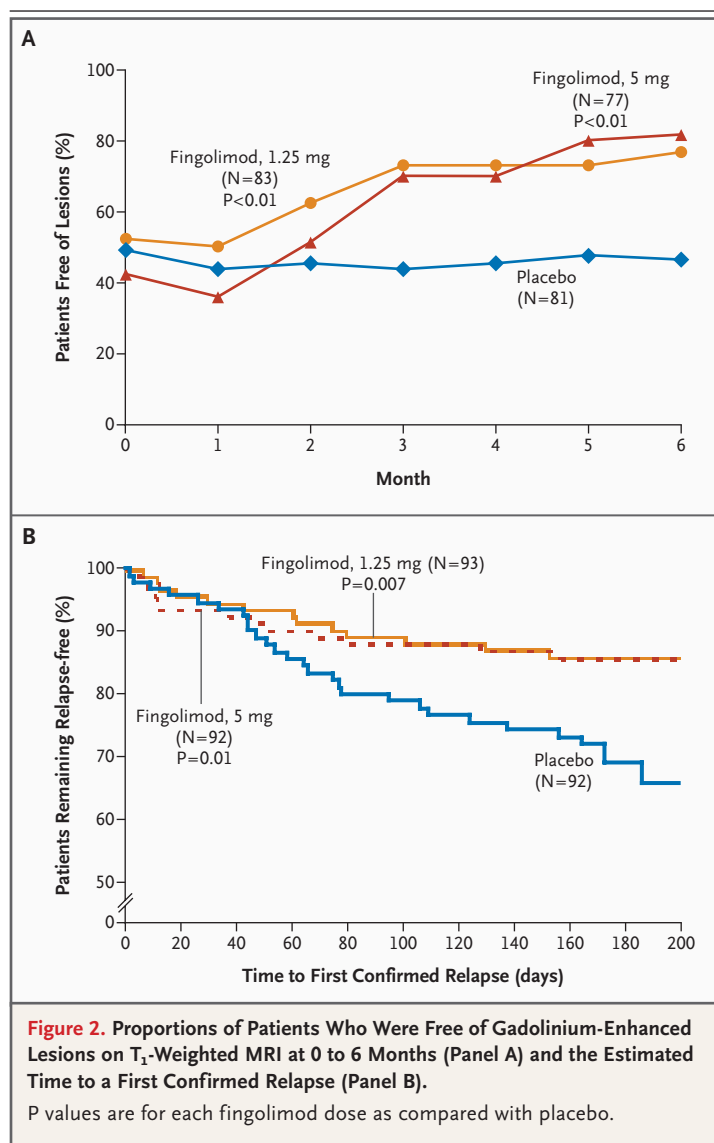
End Point	Placebo	Fingolimod, 1.25 mg	Fingolimod, 5.0 mg	P Value	
				1.25 mg vs. Placebo	5.0 mg vs. Placebo
Clinical (intention-to-treat population)					
No. evaluated	92	93	92		
Annualized relapse rate	0.77	0.35	0.36	0.009	0.01
Relative reduction in relapse rate vs. placebo — % (95% CI)*		55 (18 to 75)	53 (14 to 74)		
Patients free of relapse at 6 mo — %†	66	86	86	0.003	0.004
Confirmed relapses — no.	34	16	16		
All relapses — no.	40	21	18		
Confirmed relapses with complete clinical recovery — no. (%)	12 (35)	12 (75)	7 (44)		
Patients who received corticosteroid therapy					
No. (%)	23 (25)	11 (12)	10 (11)	0.02	0.02
Cumulative dose (mg/kg of body weight)	2372	848	725	0.20	0.19
No. of hospitalizations due to relapse	4	2	1		
EDSS score‡					
Mean	2.7	2.6	2.6	0.74	0.64
Median (range)	2.3 (0 to 7.0)	2.0 (0 to 6.5)	2.0 (0 to 6.0)		
Categorical change from baseline in EDSS score — no./total no. (%)§					
Improved or stable	71/89 (80)	84/93 (90)	75/88 (85)	0.06	0.43
Worse	18/89 (20)	9/93 (10)	13/88 (15)		

* Data are from the Poisson regression model. CI denotes confidence interval.

† Data are Kaplan–Meier estimates.

‡ Scores range from 0 to 10; higher scores indicate a higher degree of disability.

§ The change in the EDSS score could not be calculated for seven patients because of missing scores at baseline, at 6 months, or both. Improvement was defined as a decrease of 1.0 point or more, stable condition as a change of no more than half a point, and worsening as an increase of 1.0 point or more.



month 12, whereas 65 to 67% were free of relapse in the groups given placebo and fingolimid. The EDSS scores did not worsen during 12 months of treatment.

ADVERSE EVENTS

In the core study, the incidence of adverse events was higher in the group of patients who received fingolimid at a dose of 5.0 mg per day than in the group that received the 1.25-mg dose and the placebo group (Table 4). Frequently reported adverse events associated with fingolimid were nasopharyngitis and dyspnea (both mainly in the group of patients who received fingolimid at a dose of 5.0 mg), headache, diarrhea, and nausea.

The study medication was discontinued because of adverse events in four patients who received placebo, in five patients who received 1.25 mg of fingolimid, and in eight patients who received 5.0 mg of fingolimid. The incidence of serious adverse events was similar among the study groups (Table 4); no patient died.

The overall incidence of adverse events in the extension study was lower than that in the core study, with nasopharyngitis, influenza, and headache reported most frequently (Table 5). No infections were reported as serious adverse events in the core study. Two infections were reported as serious adverse events during the extension: one case of facial herpes zoster in a patient who switched from placebo to fingolimid at a dose of 5.0 mg and one case of enterocolitis in a patient who switched from placebo to fingolimid at a dose of 1.25 mg.

In the core study, after 10 weeks of treatment with fingolimid at a dose of 5.0 mg, the posterior reversible encephalopathy syndrome developed in a 52-year-old woman. This syndrome was characterized clinically by headache, acute cortical blindness, ophthalmoplegia, dysarthria, and ataxia. MRI showed diffuse areas of hyperintensity in the occipital region and brain stem on T₂-weighted scans — findings consistent with the presence of posterior reversible encephalopathy syndrome.^{31,32} The patient did not have a history of hypertension or renal disease. Neurologic symptoms and the hyperintense areas on MRI began to improve 72 hours after the discontinuation of treatment, leaving a residual right homonymous hemianopia corresponding to a left occipital hyperintensity and mild ataxia, which did not change after 15 months of follow-up.

Clinically asymptomatic lymphopenia and increases in liver enzyme levels (mainly alanine aminotransferase) were the most common laboratory abnormalities. Peripheral-blood lymphocyte counts decreased rapidly to approximately 20 to 30% of the baseline value in both fingolimid groups. During the core study, an increase in the alanine aminotransferase level to three or more times the upper limit of the normal range (≥ 90 U per liter in women and ≥ 117 U per liter in men) was more frequent with fingolimid (in 10% of the patients who received 1.25 mg and in 12% of those who received 5 mg) than with placebo (1%; $P=0.02$ and $P<0.005$, respectively). Elevations of aspartate aminotransferase levels were

Table 3. MRI and Clinical End Points in the Extension Study.

Variable	Placebo and Fingolimod, 1.25 mg (N=28)	Placebo and Fingolimod, 5.0 mg (N=32)	Fingolimod, 1.25 mg (N=62)	Fingolimod, 5.0 mg (N=65)
MRI (primary MRI analysis population)*				
No. of gadolinium-enhanced lesions				
Mo 6 (extension baseline)				
Mean ±SD	2.9±5.2	1.6±2.6	1.2±6.2	0.3±0.6
Median (range)	1.0 (0–26)	0.0 (0–9)	0.0 (0–48)	0.0 (0–3)
Mo 12				
Mean ±SD	0.2±0.6	0.4±0.7	1.0±6.4	0.2±0.5
Median (range)	0.0 (0–3)	0.0 (0–3)	0.0 (0–50)	0.0 (0–2)
P value (within group, mo 6 vs. mo 12)	P<0.001	P=0.004	P=0.34	P=0.24
Patients free of gadolinium-enhanced lesions at mo 12 — no. (%)	24 (86)	22 (69)	53 (85)	57 (88)
New T ₂ lesions, mo 7–12				
Mean ±SD	0.5±1.0	0.9±1.5	1.1±4.6	0.6±1.1
Median (range)	0.0 (0–4)	0.0 (0–6)	0.0 (0–35)	0.0 (0–4)
Patients with no new T ₂ -weighted lesions, mo 7–12 (%)†	19 (68)	18 (56)	45 (73)	47 (73)
Clinical (extension intention-to-treat population)‡				
Annualized relapse rate, mo 0–6	0.70	0.69	0.36	0.32
Annualized relapse rate, mo 7–12	0.21	0.10	0.29	0.23
Clinical (intention-to-treat population)				
Annualized relapse rate, mo 0–12			0.31	0.29
Patients free of relapse at mo 12 (%)§	67	65	79	79
EDSS score at mo 12¶				
Mean ±SD	2.4±1.4	2.7±1.4	2.5±1.4	2.6±1.6
Median (range)	2.0 (0.0–6.5)	2.0 (1.0–6.0)	2.0 (0.0–6.0)	2.0 (0.0–6.5)

* The population with data that could be evaluated from the extension study consisted of patients who were considered to have data that could be evaluated within the core study, who did not discontinue the study drug prematurely, and who had had an MRI scan at month 12.

† Data were not available for one patient in the 5.0-mg group.

‡ The intention-to-treat population in the extension group included patients who received at least 1 dose of fingolimod during months 7 through 12: 40 patients who switched from placebo to the 1.25-mg dose, 43 who switched from placebo to the 5.0-mg dose, 87 who received the 1.25-mg dose in the core and extension studies, and 80 who received the 5.0-mg dose in both studies.

§ Data, which are based on Kaplan–Meier estimates, were available for 40 patients who switched from placebo to the 1.25-mg dose, 43 who switched from placebo to the 5.0-mg dose, 93 who received the 1.25-mg dose in the core and extension studies, and 92 who received the 5.0-mg dose in both studies.

¶ Scores for the Expanded Disability Status Scale (EDSS) range from 0 to 10; higher scores indicate a greater degree of disability. Data were available for 37 patients who switched from placebo to the 1.25-mg dose, 37 who switched from placebo to the 5.0-mg dose, 80 who received the 1.25-mg dose in the core and extension studies, and 74 who received the 5.0-mg dose in both studies.

uncommon (Table 4), and fingolimod treatment was not associated with elevations of bilirubin or alkaline phosphatase levels (see the Supplementary Appendix, available with the full text of this article at www.nejm.org). Among the 26 patients who received continuous treatment with fingolimod and had alanine aminotransferase

levels that were three or more times the upper limit of the normal range, the levels returned to less than three times the upper limit in 13 (to the normal range in 5) without any dose adjustments. Fingolimod was discontinued in the other 13 patients, and alanine aminotransferase levels subsequently returned to less than three times the

Table 4. Adverse Events in the Safety Population of the 6-Month Core Study.

Adverse Event	Placebo (N=93)	Fingolimod, 1.25 mg (N=94)		Fingolimod, 5.0 mg (N=94)	
		<i>no. of patients (%)</i>			
Any event	76 (82)	79 (84)		90 (96)*	
Most frequent events†					
Nasopharyngitis	14 (15)	16 (17)		26 (28)*	
Headache	13 (14)	22 (23)		18 (19)	
Dyspnea	1 (1)	4 (4)		12 (13)*	
Diarrhea	2 (2)	9 (10)		11 (12)*	
Nausea	2 (2)	8 (9)		10 (11)*	
Back pain	3 (3)	4 (4)		8 (9)	
Fatigue	9 (10)	8 (9)		8 (9)	
Increase in alanine aminotransferase					
Reported by investigator	2 (2)	6 (6)		7 (7)	
Confirmed‡	1 (1)	9 (10)*		11 (12)*	
Dizziness	5 (5)	2 (2)		7 (7)	
Influenza	3 (3)	6 (6)		7 (7)	
Pyrexia	1 (1)	3 (3)		7 (7)	
Constipation	3 (3)	1 (1)		6 (6)	
Somnolence	0	3 (3)		6 (6)*	
Upper abdominal pain	2 (2)	7 (7)		5 (5)	
Gastroenteritis	0	3 (3)		5 (5)	
Hypertension	1 (1)	2 (2)		5 (5)	
Leukopenia	0	2 (2)		5 (5)	
Pain in extremity	4 (4)	4 (4)		5 (5)	
Rash	3 (3)	2 (2)		5 (5)	
Arthralgia	6 (6)	5 (5)		3 (3)	
Depression	6 (6)	3 (3)		3 (3)	
Pharyngitis	2 (2)	7 (7)		3 (3)	
Paresthesia	2 (2)	5 (5)		2 (2)	
Asthenia	6 (6)	3 (3)		1 (1)	
Increase in aspartate aminotransferase					
Reported by investigator	0	1 (1)		2 (2)	
Confirmed‡	0	2 (2)		1 (1)	

upper limit of the normal range in all 13. Of four patients in whom fingolimod treatment was resumed, three had alanine aminotransferase levels that remained lower than three times the upper limit of the normal range; treatment with fingolimod was discontinued permanently in one patient. During the core and extension studies, treatment was permanently discontinued in two patients because of elevated liver enzyme levels.

No elevations in liver enzyme levels were associated with clinical symptoms.

Within 6 hours after the first dose of fingolimod, the heart rate was reduced by a mean of 13.8 and 16.6 beats per minute in the 1.25-mg and 5.0-mg groups, respectively, returning toward the baseline value with continued treatment. Symptomatic bradycardia was reported in one patient who received fingolimod at a dose

Table 4. (Continued.)

Adverse Event	Placebo (N=93)	Fingolimod, 1.25 mg (N=94)		Fingolimod, 5.0 mg (N=94)
		<i>no. of patients (%)</i>		
Serious events				
Bradycardia	0	0		3 (3)
Chest pain	0	1 (1)		2 (2)
Dyspnea	0	0		1 (1)
Endometriosis	0	0		1 (1)
Extra systoles	0	0		1 (1)
Hypertension	0	0		1 (1)
Lower-limb fracture	0	0		1 (1)
Ovarian cyst	0	0		1 (1)
Posterior reversible encephalopathy syndrome	0	0		1 (1)
Squamous-cell carcinoma	0	0		1 (1)
Ventricular extra systoles	0	0		1 (1)
Anxiety	0	1 (1)		0
Upper abdominal pain	0	1 (1)		0
Reported increase in alanine aminotransferase	0	1 (1)		0
First-degree atrioventricular block	0	1 (1)		0
Cholelithiasis	0	1 (1)		0
Jaundice	0	1 (1)		0
Neck pain	0	1 (1)		0
Benign breast neoplasm	1 (1)	0		0
Injury	1 (1)	0		0
Limb injury	1 (1)	0		0
Relapsing multiple sclerosis	1 (1)	0		0
Traffic accident	1 (1)	0		0
Suicide attempt	1 (1)	0		0
Treatment discontinued because of adverse event	4 (4)	5 (5)		8 (9)

* $P < 0.05$ for the comparison with the placebo group.

† This category includes adverse events reported in at least 5% of patients in any group. Adverse events and serious adverse events are listed in descending frequency for the group of patients who received fingolimod at a dose of 5.0 mg.

‡ A confirmed increase was defined by a value that was at least three times the upper limit of the normal range at any time on the basis of central laboratory results.

of 1.25 mg after switching from placebo and in three patients who received fingolimod at a dose of 5.0 mg; no cases of symptomatic bradycardia were reported among patients who received placebo. All episodes occurred within 24 hours after administration of the first dose and resolved spontaneously. Holter electrocardiographic monitoring was performed in 31 patients who received placebo, 31 patients who received fingolimod at

a dose of 1.25 mg, and 34 patients who received fingolimod at a dose of 5.0 mg. These assessments confirmed that the maximal decrease in the heart rate in the patients treated with fingolimod, as compared with those who received placebo, occurred within the first 6 hours. Transient second-degree Wenckebach atrioventricular block occurred in four patients who received fingolimod at a dose of 1.25 mg (in one patient only at

Table 5. Adverse Events in the Safety Population of the Extension Study.

Adverse Event	Placebo and Fingolimod, 1.25 mg (N=40)	Placebo and Fingolimod, 5.0 mg (N=43)	Fingolimod, 1.25 mg (N=87)	Fingolimod, 5.0 mg (N=80)
	<i>no. of patients (%)</i>			
Any event	31 (78)	36 (84)	63 (72)	68 (85)
Most frequent events*				
Nasopharyngitis	3 (8)	5 (12)	11 (13)	14 (18)
Influenza	5 (12)	4 (9)	7 (8)	9 (11)
Leukopenia	1 (2)	1 (2)	4 (5)	7 (9)
Headache	4 (10)	5 (12)	10 (11)	6 (8)
Lymphopenia	1 (2)	3 (7)	9 (10)	6 (8)
Decreased lymphocyte count	1 (2)	1 (2)	2 (2)	5 (6)
Upper respiratory tract infection	0	0	1 (1)	5 (6)
Asthenia	0	2 (5)	0	4 (5)
Asthma	0	1 (2)	0	4 (5)
Bronchitis	1 (2)	0	2 (2)	4 (5)
Increase in alanine aminotransferase				
Reported by investigator	1 (2)	4 (9)	4 (5)	3 (4)
Confirmed†	3 (8)	2 (5)	3 (3)	3 (4)
Arthralgia	0	3 (7)	1 (1)	3 (4)
Depression	0	4 (9)	4 (5)	3 (4)
Cough	1 (2)	3 (7)	5 (6)	2 (2)
Diarrhea	0	3 (7)	5 (6)	2 (2)
Migraine	2 (5)	3 (7)	0	2 (2)
Back pain	1 (2)	3 (7)	2 (2)	1 (1)
Fatigue	3 (7)	2 (5)	3 (3)	1 (1)
Pharyngitis	2 (5)	1 (2)	3 (3)	1 (1)
Increase in aspartate aminotransferase				
Reported by investigator	0	3 (7)	1 (1)	0
Confirmed†	0	0	0	0
Dizziness	0	3 (7)	1 (1)	0
Hyperhidrosis	2 (5)	0	0	0
Palpitations	2 (5)	1 (2)	0	0
Tendonitis	2 (5)	0	0	0

baseline, in one at baseline and day 1, and in two on day 1) and five patients who received fingolimod at a dose of 5.0 mg (all on day 1). All Holter assessments at 3 months were normal in the patients who received placebo and in those who received fingolimod at a dose of 1.25 mg; a single episode of nonsustained ventricular tachycardia (four beats) was reported on one tracing in a patient who received fingolimod at a dose of 5.0 mg. There was an initial reduction in mean blood pres-

sure (5 to 6 mm Hg lower than the baseline value) within 4 to 5 hours after the administration of fingolimod, followed by a sustained elevation (4 to 6 mm Hg higher than the baseline value) after 2 months of treatment, with no further increase during the extension study (data not shown).

During the core study, pulmonary-function tests showed a reduction in FEV₁ in the group of patients who received fingolimod at a dose of 5.0 mg, as compared with the placebo group.

Table 5. (Continued.)

Adverse Event	Placebo and Fingolimod, 1.25 mg (N=40)	Placebo and Fingolimod, 5.0 mg (N=43)	Fingolimod, 1.25 mg (N=87)	Fingolimod, 5.0 mg (N=80)
	<i>no. of patients (%)</i>			
Serious adverse events				
Any	2 (5)	3 (7)	2 (2)	6 (8)
Asthma	0	0	0	2 (2)
Adrenal mass	0	0	0	1 (1)
Neutropenia	0	0	0	1 (1)
Pregnancy	0	0	0	1 (1)
Salpingitis	0	0	0	1 (1)
Abdominal pain	0	1 (2)	0	0
Arrhythmia	1 (2)	0	0	0
Bradycardia	1 (2)	0	0	0
Bronchospasm	0	1 (2)	0	0
Enterocolitis	1 (2)	0	0	0
Abnormal heart rate	1 (2)	0	0	0
Hepatitis	0	0	1 (1)	0
Herpes zoster	0	1 (2)	0	0
Relapsing multiple sclerosis	0	0	1 (1)	0
Nausea	0	1 (2)	0	0
Otitis externa	0	1 (2)	0	0
Palpitations	1 (2)	0	0	0
Treatment discontinued because of an adverse event	1 (2)	4 (9)	4 (5)	5 (6)

* This category includes adverse events occurring in at least 5% of patients in any group. Adverse events and serious adverse events are listed in descending frequency for the group of patients who received fingolimod at a dose of 5.0 mg.

† A confirmed increase was defined by a value that was at least three times the upper limit of the normal range at any time on the basis of central laboratory results.

The average reduction from baseline in the percentage of predicted FEV₁ at month 6 was 1.9% in the placebo group (37 patients), as compared with 8.8% (P=0.003) in the group of patients who received fingolimod at a dose of 5.0 mg (35 patients) and 2.8% (P=0.68) in the group of patients who received fingolimod at a dose of 1.25 mg (40 patients). After 6 months of treatment, as compared with an increase of 4.3% of the predicted FVC in the placebo group, the FVC was decreased by 0.8% in the group of patients who received fingolimod at a dose of 1.25 mg and by 3.2% of the predicted value in the group of patients who received fingolimod at a dose of 5.0 mg (P<0.05 for both comparisons with placebo). In both groups of patients who received fin-

golimod, the carbon monoxide diffusion capacity did not differ from that in the patients who received placebo. In the extension study, there was no further change in FEV₁, FVC, or the carbon monoxide diffusion capacity at month 12, as compared with month 6, in any of the groups (those who received continuous fingolimod or those who switched from placebo to fingolimod; data not shown). No increase in clinical respiratory adverse events was reported in the group of patients who received fingolimod at a dose of 1.25 mg, as compared with the placebo group. There were more reports of dyspnea in the group of patients who received fingolimod at a dose of 5.0 mg than in the placebo group (Table 4). During the extension study, dyspnea was rarely reported (no re-

ports in the group of patients who received continuous treatment with fingolimod at a dose of 1.25 mg and one report each in the other three groups).

DISCUSSION

Our results demonstrate that oral fingolimod given once daily provides significant and rapid improvement in MRI measures of inflammation and in relapse-related clinical end points in patients with relapsing multiple sclerosis. Patients who received placebo also had marked improvements after switching to the active drug in the extension study.

These clinical and MRI results suggest that the main mechanism of action of fingolimod — sequestration of lymphocytes in secondary lymphoid organs through an interaction with G protein-coupled receptors for sphingosine-1-phosphate¹⁵ — has a favorable effect on the course of relapsing multiple sclerosis. Additional mechanisms may also be involved. These mechanisms may be related to binding to other sphingosine-1-phosphate receptors — also expressed in neural cells³³⁻³⁶ — and to the high availability of fingolimod within the central nervous system because of its lipophilic nature. The observation that the 1.25-mg dose was as effective as the 5.0-mg dose, in terms of both MRI findings and relapse rates, provides evidence of a need to explore the effects of a lower dose in future trials.

The most frequently reported adverse events associated with fingolimod were upper respiratory tract infections (mainly nasopharyngitis). Two serious infections were reported in patients who were given fingolimod, and larger trials are needed for a full assessment of the risk of serious infections with fingolimod therapy. Similarly, the risk of the posterior reversible encephalopathy syndrome needs to be quantified; in our study it occurred in one patient who was given fingolimod. The pathogenesis of this syndrome is unclear but seems to be related to impaired autoregulation and endothelial function. It has been associated with hypertension, eclampsia, and the use of several immunosuppressive and immunomodulating agents, including interferon alfa and immune globulins administered intravenously.^{31,32}

The importance of elevated liver enzyme levels observed in this study requires further evalu-

ation in longer-term studies. Liver enzyme abnormalities were not found in transplantation studies. In these studies, fingolimod was administered as an add-on therapy to cyclosporine,³⁷ and its hepatic effects may therefore have been disguised by concomitant treatment with this agent, which is known to cause elevated aminotransferase levels. The dose-dependent decline in the heart rate observed in the first hours after the first dose has also been reported in studies of transplantation.³⁷⁻³⁹ We observed other adverse events related to the pharmacologic characteristics of fingolimod, including decreases in forced expiratory flow and increases in respiratory symptoms and blood pressure.

Our results show that oral fingolimod may be a treatment option for relapsing multiple sclerosis. Before these findings can be considered clinically directive, the benefits and risks of fingolimod need to be further evaluated in larger-scale, longer-term clinical studies.

Supported by Novartis Pharma, Basel, Switzerland.

Dr. Kappos reports having participated as principal investigator, member, or chair of planning and steering committees or advisory boards in clinical trials of multiple sclerosis sponsored by Abbott, Bayer, Bayhill, Berlex, Biogen Idec, Boehringer Ingelheim, Bristol-Myers Squibb, Centocor, Eisai, Elan, Genzyme, GlaxoSmithKline, Immune Response, Neurocrine, Novartis, Sanofi-Aventis, Schering, Serono, Roche, Teva, UCB Pharma, and Wyeth and having received lecture fees from one or more of the above-listed companies. Dr. Antel reports having received remuneration for consulting, participation in clinical trials, and advisory board and steering committee membership from Aegera, Aventis, Bayhill, Berlex, Biogen Idec, BioMS, Boehringer Ingelheim, Genentech, Immune Response, Neurocrine Biosciences, Novartis, Schering-Plough, Serono, and Teva Neuroscience. Dr. Comi reports having received consulting fees from Serono, Schering, Teva, Novartis, Sanofi-Aventis, Biogen and Wyeth; grant support from Teva and Serono; and lecture fees from Teva, Serono, and Schering. Dr. Radue reports having received grant support and lecture fees from Biogen Idec, Schering, Novartis, Sanofi-Aventis, and GlaxoSmithKline for evaluation of multicenter studies of multiple sclerosis, as well as payments for advisory-board and steering-committee membership. Dr. Montalban reports having received consulting fees from Biogen Idec, Sanofi-Aventis, Novartis, Serono, Schering, and Wyeth; lecture fees from Biogen, Schering, Sanofi-Aventis and Serono; and grant support from Biogen Idec, Sanofi-Aventis, Serono and Schering. Dr. O'Connor reports having received consulting fees from Biogen Idec, Bristol-Myers Squibb, Sanofi-Aventis, Novartis, Serono, Schering, and Wyeth; lecture fees from Biogen Idec; and grant support from Biogen Idec, Novartis, Sanofi-Aventis, Schering, BioMS, Bristol-Myers Squibb, and Genentech. Dr. Polman reports having received consulting fees from Biogen Idec, Schering, Teva, Serono, Novartis, GlaxoSmithKline, and Antisense Therapeutics; lecture fees from Biogen Idec, Schering, and Teva; and grant support from Biogen Idec, Schering, Wyeth, and GlaxoSmithKline. Drs. Haas, Korn, and Karlsson are employees of Novartis; Drs. Korn and Karlsson report owning shares in Novartis. No other potential conflict of interest relevant to this article was reported.

APPENDIX

The following people participated in the study (names of principal investigators are in bold): *Data and Safety Monitoring Board* — C. Polman (chair), Vrije Universiteit Medical Center, Amsterdam; J. Camm, St. George's Hospital Medical School, London; M. Daumer, Sylvia Lawry Centre for Multiple Sclerosis Research, Munich; F. Lublin, Corinne Goldsmith Dickinson Center for Multiple Sclerosis, New York; *Steering Committee* — L. Kappos (chair), University Hospital, Basel; J. Antel, Le Centre Universitaire de Santé McGill, Montreal Neurological Institute, McGill University, Montreal; G. Comi, San Raffaele Hospital, Milan; A. Korn, Novartis Pharmaceuticals Corporation, East Hanover, NJ; X. Montalban, Hospital Vall d'Hebron, Barcelona; P. O'Connor, St. Michael's Hospital, Toronto; E.W. Radue, University Hospital, Basel; *Study Group* — *Canada*: J. Antel, L. Durcan, A. Baror, Le Centre Universitaire de Santé McGill, Montreal Neurological Institute, McGill University, Montreal; P. Duquette, G. Bernier, Centre Hospitalier Universitaire-Notre-Dame Hospital, Montreal; M. Freedman, H. MacLean, F. Costello, Ottawa Hospital, Ottawa; P. O'Connor, T.A. Gray, M. Hohol, St. Michael's Hospital, Toronto; J. Oger, S. Hashimoto, V. Devonshire, UBC Hospital, Vancouver; *Denmark*: P.S.G. Sørensen, P. Datta, J.C. Faber-Rod, Neurocentret, Rigshospitalet, Copenhagen; J. Frederiksen, S. Knudsen, V. Petreanaite, Kobenhavns Amts Sygehus, Glostrup; *Finland*: M. Färkkilä, J. Halavaara, H. Harno, Postitalon Lääkäriasema Oy, Helsinki; I. Elovaara, H. Kuusisto, J. Palmio, Finn-Medi Tutkimus Oy, Tampere; L. Airas, V. Kaasinen, M. Laaksonen, Turku University Hospital, Turku; *France*: P. Vermersch, Hôpital Roger Salengro, Lille; J. Pelletier, L. Feuillet, L. Suchet, Hôpital de la Timone, Marseille; *Germany*: E. Mauch, C. Gunser, K. Oberbeck, Akademisches KH der Universität Ulm, Schwendi; P. Rieckmann, M. Buttman, M. Klein, Julius-Maximilians-Universität, Würzburg; *Italy*: A. Ghezzi, M. Zaffaroni, S. Baldini, Ospedale S. Antonio Abate, Gallarate; G. Mancardi, F. Cioli, E. Capello, Ospedale S. Martino Università degli Studi di Genova, Genoa; G. Comi, L. Maiola, F. Esposito, San Raffaele Hospital, Milan; C. Pozzilli, E. Onesti, S. Romano, Ospedale Sant'Andrea Università La Sapienza, Rome; *Poland*: A. Czlonkowska, T. Litwin, L. Darda-Ledzion, Instytut Psychiatrii i Neurologii, Warsaw; H. Kwiecinski, M. Golebiowski, A. Podlecka, Klinika Neurologii AM, Warsaw; *Portugal*: L. Cunha, F. Matias, M. do Carmo Macario, Hospitais da Universidade de Coimbra, Coimbra; R. Pedrosa, M. Almeida, J. Esteves Pena, Hospital Sto. António dos Capuchos, Lisbon; J. de Sa, J. Buerra da Costa, J. Ferreira, Hospital de Santa Maria, Centro de estudos Egas Moniz, Lisbon; *Spain*: T. Arbizu, O. Carmona, V. Casado, Ciutat Sanitària i Universitària de Bellvitge, Barcelona; X. Montalban, M. Tintore, R. Pelayo, Hospital Vall d'Hebron, Barcelona; R. Arroyo, M. Bartolome, V. De las Heras, Hospital Clinico San Carlos, Madrid; B. Casanova, I. Bosca, Hospital La Fe, Valencia; O. Fernandez, A. Leon, F. Romero, Hospital Carlos Haya, Malaga; G. Izquierdo, M. Gamero, J. Maria Garcia, Hospital Virgen de la Macarena, Seville; *Switzerland*: L. Kappos, J. Kuhle, L. Achtnichts, University Hospital, Basel; N. Goebels, C. Skulina, J. Waskoenig, University Hospital, Zurich; *United Kingdom*: D. Bates, P. Nichols, Royal Victoria Infirmary, Newcastle-upon-Tyne; *MS-MRI Evaluation Center*: University Hospital, Basel; E.W. Radue, A. de Vera, Novartis Pharma, Basel, Switzerland, and East Hanover, NJ: O. Bettoni-Ristic, P. Burtin, R. Preiss, S. Wehr, T. Zubal.

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