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A Placebo-Controlled Trial of Oral Fingolimod in Relapsing Multiple Sclerosis

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ABSTRACT

BACKGROUND

Oral fingolimod, a sphingosine-1-phosphate–receptor modulator that prevents the egress of lymphocytes from lymph nodes, significantly improved relapse rates and end points measured on magnetic resonance imaging (MRI), as compared with either placebo or intramuscular interferon beta-1a, in phase 2 and 3 studies of multiple sclerosis.

METHODS

In our 24-month, double-blind, randomized study, we enrolled patients who had relapsing–remitting multiple sclerosis, were 18 to 55 years of age, had a score of 0 to 5.5 on the Expanded Disability Status Scale (which ranges from 0 to 10, with higher scores indicating greater disability), and had had one or more relapses in the previous year or two or more in the previous 2 years. Patients received oral fingolimod at a dose of 0.5 mg or 1.25 mg daily or placebo. End points included the annualized relapse rate (the primary end point) and the time to disability progression (a secondary end point).

RESULTS

A total of 1033 of the 1272 patients (81.2%) completed the study. The annualized relapse rate was 0.18 with 0.5 mg of fingolimod, 0.16 with 1.25 mg of fingolimod, and 0.40 with placebo ($P<0.001$ for either dose vs. placebo). Fingolimod at doses of 0.5 mg and 1.25 mg significantly reduced the risk of disability progression over the 24-month period (hazard ratio, 0.70 and 0.68, respectively; $P=0.02$ vs. placebo, for both comparisons). The cumulative probability of disability progression (confirmed after 3 months) was 17.7% with 0.5 mg of fingolimod, 16.6% with 1.25 mg of fingolimod, and 24.1% with placebo. Both fingolimod doses were superior to placebo with regard to MRI-related measures (number of new or enlarged lesions on T_2-weighted images, gadolinium-enhancing lesions, and brain-volume loss; $P<0.001$ for all comparisons at 24 months). Causes of study discontinuation and adverse events related to fingolimod included bradycardia and atrioventricular conduction block at the time of fingolimod initiation, macular edema, elevated liver-enzyme levels, and mild hypertension.

CONCLUSIONS

As compared with placebo, both doses of oral fingolimod improved the relapse rate, the risk of disability progression, and end points on MRI. These benefits will need to be weighed against possible long-term risks. (ClinicalTrials.gov number, NCT00289978.)

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Fingolimod (FTY720) is an oral sphingosine-1-phosphate–receptor modulator[1] that is currently being evaluated for the treatment of multiple sclerosis. There is evidence that fingolimod acts by preventing lymphocyte egress from lymph nodes.[2,3] This leads to a reduced infiltration of potentially autoaggressive lymphocytes into the central nervous system.[4,5] Preclinical findings also suggest that fingolimod may promote neuroprotective and reparative processes within the central nervous system through modulation of sphingosine-1-phosphate receptors expressed on neural cells.[6-12]

A 6-month, phase 2, placebo-controlled study[13] and its open-label extension study[14] showed sustained suppression, for up to 5 years, of both relapse and inflammatory activity in patients receiving fingolimod. Furthermore, in a recently completed, 12-month, phase 3 study involving patients with relapsing–remitting multiple sclerosis (TRANSFORMS [Trial Assessing Injectable Interferon vs. FTY720 Oral in RRMS]; ClinicalTrials.gov number, NCT00340834), reported elsewhere in this issue of the *Journal*, fingolimod reduced the relapse rate and disease activity as measured with the use of magnetic resonance imaging (MRI), as compared with a once-weekly, intramuscular injection of interferon beta-1a at a dose of 30 μg.[15]

In our phase 3, double-blind, placebo-controlled study, called FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis), we investigated the effects of daily fingolimod treatment for 24 months on the relapse rate, disability progression, and MRI measures of inflammation, burden of disease, and tissue destruction in patients with relapsing–remitting multiple sclerosis.

Methods

Study Oversight

Steering-committee members (listed in the Supplementary Appendix, available with the full text of this article at NEJM.org) collaborated with the sponsor, Novartis Pharma, to develop the protocol and monitor the ongoing study. Data were collected by the investigators and analyzed by the sponsor. All the authors had access to the data, participated in the data analysis and interpretation, and wrote the manuscript. All authors vouch for the accuracy and completeness of the data and the statistical analysis. All authors participated in the writing of the manuscript and approved the final manuscript before submitting it for publication.

Patients

Key eligibility criteria were an age of 18 to 55 years; a diagnosis of multiple sclerosis, according to the revised McDonald criteria[16]; a relapsing–remitting course[17]; one or more documented relapses in the previous year or two or more in the previous 2 years; and a score of 0 to 5.5 on the Expanded Disability Status Scale (EDSS; which ranges from 0 to 10, with higher scores indicating greater disability).[18] Key exclusion criteria were relapse or corticosteroid treatment within 30 days before randomization, active infection, macular edema, diabetes mellitus, immune suppression (drug- or disease-induced), or clinically significant systemic disease. Interferon-beta or glatiramer acetate therapy had to have been stopped 3 or more months before randomization.

The study was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice[19] and the Declaration of Helsinki.[20] The protocol was approved by each site's institutional review board; patients gave written informed consent before any study-related procedures were performed.

Study Design and Randomization

Patients were randomly assigned, in a 1:1:1 ratio, to receive oral fingolimod capsules in a dose of 0.5 mg or 1.25 mg or matching placebo, once daily for 24 months. Randomization was performed centrally, with the use of a validated system and stratification according to site, with a block size of six within each site.

To ensure that all assessments remained unbiased regarding the study-group assignments (i.e., unaffected by awareness of them), an independent, specially trained and certified[21] examining neurologist determined all the EDSS scores; this examining neurologist or a trained technician administered the Multiple Sclerosis Functional Composite (MSFC; comprising the average of the scores on the timed 25-foot walk, the 9-hole peg test, and the paced auditory serial-addition test with a 3-second interstimulus interval, with each converted to a z score [with the combined study population at baseline as the reference population], with higher scores representing improve-

ment).[22] Another independent physician monitored patients for 6 or more hours after administration of the first dose of the study drug. MRI scans were analyzed at a central MRI evaluation center by radiologists who were unaware of the study-group assignments, and an independent data and safety monitoring board evaluated the safety and overall benefit–risk profiles.

STUDY PROCEDURES AND END POINTS

Clinical assessments were performed at screening and at randomization (baseline), and study visits, including safety assessments, were scheduled at 2 weeks and 1, 2, 3, 6, 9, 12, 15, 18, 21, and 24 months after randomization. The EDSS score was determined every 3 months, and the MSFC z score every 6 months. Standardized MRI scans were obtained at the screening visit and at 6, 12, and 24 months and were analyzed centrally at the Multiple Sclerosis–MRI Evaluation Center at the University Hospital in Basel, Switzerland.

The primary end point was the annualized relapse rate, defined as the number of confirmed relapses per year. Relapses were verified by the examining neurologist within 7 days after the onset of symptoms. To constitute a confirmed relapse, the symptoms must have been accompanied by an increase of at least half a point in the EDSS score, of one point in each of two EDSS functional-system scores, or of two points in one EDSS functional-system score (excluding scores for the bowel–bladder or cerebral functional systems).

The key secondary end point was the time to confirmed disability progression, defined as an increase of one point in the EDSS score (or half a point if the baseline EDSS score was equal to 5.5), confirmed after 3 months, with an absence of relapse at the time of assessment and with all EDSS scores measured during that time meeting the criteria for disability progression.

Other secondary end points included the time to a first relapse, time to disability progression (confirmed after 6 months), changes in the EDSS score and MSFC z score[23] between baseline and 24 months, number of gadolinium-enhancing lesions, proportion of patients free from gadolinium-enhancing lesions, number of new or enlarged lesions on T_2-weighted MRI scans, proportion of patients free from new or enlarged lesions on T_2-weighted scans, volumes of hyperintense lesions on T_2-weighted scans and hypointense lesions on T_1-weighted scans, change in brain volume between baseline and 24 months, and safety and tolerability measures. Specifications of the adverse-event monitoring procedure, as defined in the study protocol, were the same as those in TRANSFORMS and are detailed in the Supplementary Appendix, which also provides other methodologic details.

STATISTICAL ANALYSIS

For the primary end point, on the basis of data from a phase 2 study of fingolimod,[13,24] the expected annualized relapse rate was 0.7 for the group receiving placebo and 0.42 for the group receiving 1.25 mg of fingolimod, with a common standard deviation of 1.06. We calculated that a sample of 1250 patients would provide 95% statistical power to detect a relative reduction of 40% or more in the annualized relapse rate with fingolimod as compared with placebo, after 24 months. With this sample size, using a log-rank test and a two-sided α level of 0.05 (assuming a study-discontinuation rate of 25%[13]), we calculated that the study would have a statistical power of more than 90% to detect an absolute difference between the two groups of 12% in the proportion of patients with disability progression (confirmed after 3 months) at month 24, which was expected to be approximately 30% in the placebo group.

Both the intention-to-treat population and the safety population included all patients who had undergone randomization. The study tested two null hypotheses: that there were no differences in the annualized relapse rate between the group receiving fingolimod at a dose of 1.25 mg and the group receiving placebo or between the group receiving fingolimod at a dose of 0.5 mg and the group receiving placebo. The aggregate annualized relapse rate was estimated by means of a negative binomial regression model with adjustment for study group, country, number of relapses within 2 years before baseline, and EDSS score at baseline. The time to relapse or progression was estimated with the use of the Kaplan–Meier method.[25] The times to disability progression (confirmed after 3 or 6 months) were compared in the main analysis by means of the log-rank test and in the supportive analysis by means of a Cox proportional-hazards model with adjustment for study group, country, baseline EDSS score, and age. To control for a type I statistical error, a prospectively planned, hierarchical testing procedure was used to compare fingolimod with placebo re-

garding the primary and key secondary end points, in the following order: the annualized relapse rate, first in association with 1.25 mg of fingolimod and next in association with 0.5 mg of fingolimod, and then the time to disability progression (confirmed after 3 months), first with 1.25 mg of fingolimod and next with 0.5 mg of fingolimod. Each test was performed with a significance level of 0.05. However, the next test was performed only when the preceding test was statistically significant. Missing data were not imputed.

Safety analyses were summarized by means of descriptive statistics; inferential significance testing was not performed. Statistical details for other end points are provided in the Supplementary Appendix.

RESULTS

STUDY POPULATION

From January 2006 through August 2007, a total of 1272 patients were randomly assigned to a study group (Fig. 1) at 138 centers in 22 countries (see the Supplementary Appendix for a list of the centers and principal investigators). Baseline characteristics were similar across the three study groups (Table 1). In total, 1033 patients (81.2%) completed the 24-month study, with 945 (74.3%) still receiving the assigned study drug. The study drug was discontinued in proportionately fewer patients in the group receiving 0.5 mg of fingolimod (18.8%) than in the group receiving 1.25 mg of fingolimod (30.5%) or in the placebo group (27.5%). Reasons for study-drug discontinuation are listed in Figure 1.

EFFICACY

All clinical and MRI-related efficacy end points significantly favored both doses of fingolimod over placebo, and there were no significant differences in efficacy between the two fingolimod doses (Table 2).

Relapse

The aggregate annualized relapse rate (the primary end point) was lower with fingolimod at a dose of 0.5 mg (0.18) and fingolimod at a dose of 1.25 mg (0.16) than with placebo (0.40), representing relative reductions of 54% and 60%, respectively, in the annualized relapse rate (Table 2). As compared with placebo, both doses of fingolimod reduced the annualized relapse rate among patients who had not previously received disease-modifying treatment as well as among those who had been treated previously ($P<0.01$ for all comparisons). In the fingolimod groups as compared with the placebo group, the time to a first relapse was longer (Fig. 2A), the risk of relapse was reduced, and proportionately more patients remained free of relapse during the 24-month period (Table 2).

Disability

The time to disability progression, with confirmation either after 3 months (the key secondary end point) or after 6 months, was longer with both fingolimod doses than with placebo (Fig. 2B and Table 2). Fingolimod reduced the risk of disability progression, confirmed after 3 months, over the 24-month study period (hazard ratios, 0.68 for the 1.25-mg dose and 0.70 for the 0.5-mg dose). The cumulative probability of disability progression (confirmed after 3 months) was 17.7% for 0.5 mg of fingolimod, 16.6% for 1.25 mg of fingolimod, and 24.1% for placebo. Regarding disability progression that was confirmed after 6 months, the risk was also reduced with fingolimod over the 24-month study period (hazard ratio, 0.60 with the 1.25-mg dose and 0.63 for the 0.5-mg dose), and the cumulative probability of progression was 12.5% for 0.5 mg of fingolimod, 11.5% for 1.25 mg of fingolimod, and 19.0% for placebo. During the study period, the EDSS scores and MSFC z scores remained stable or improved slightly in the fingolimod groups and worsened in the placebo group (Table 2).

MRI-Related End Points

Patients in either fingolimod group had significantly fewer gadolinium-enhancing lesions than those in the placebo group at 6, 12, and 24 months, as well as fewer new or enlarged lesions on T_2-weighted MRI scans at 24 months (Table 2). Proportionately more patients in the fingolimod groups than in the placebo group were also free from gadolinium-enhancing or new or enlarging lesions at these time points (Table 2 and Fig. 2C). The median volume of lesions on T_2-weighted scans decreased between baseline and month 24 with fingolimod but increased with placebo.

During the 24-month study period, changes in the volume of hypointense lesions on T_1-weight-

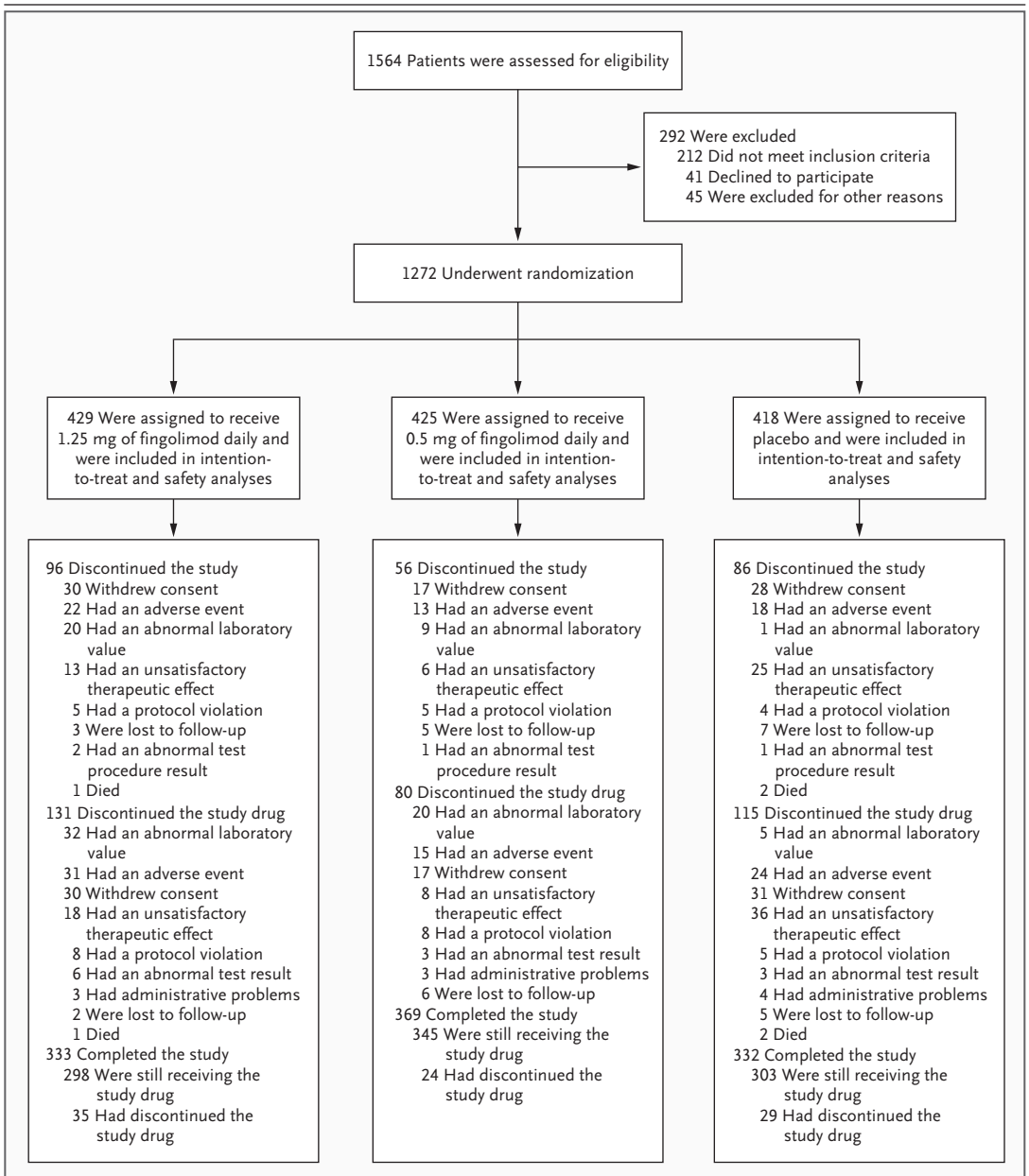

Figure 1. Enrollment, Randomization, and Follow-up of Study Patients.

Among the 292 patients who were assessed for eligibility but were not enrolled, some were excluded for more than one reason. For one patient receiving 1.25 mg of fingolimod daily who completed the study while receiving the study drug, the status was incorrectly recorded by the investigator as having discontinued the study while still receiving the study drug. Patients who discontinued the study drug include those who discontinued the study; the correct status is shown here.

ed scans favored both doses of fingolimod over placebo (Table 2). In addition, reductions in brain volume were smaller with fingolimod.

ADVERSE EVENTS

Similar proportions of patients (93 to 94%) in the three study groups were reported to have adverse events (Table 3); the events were mild to moderate in severity in 82% of patients receiving 0.5 mg of fingolimod, 77% of those receiving 1.25 mg of fingolimod, and 77% of those receiving placebo. Adverse events that led to discontinuation of the study medication (including abnormal laboratory-test results) were more common with fingolimod

Table 1. Baseline Characteristics of the Patients, According to Study Group.*

Characteristic	Fingolimod		Placebo (N=418)
	1.25 mg (N=429)	0.5 mg (N=425)	
Age — yr			
Mean	37.4±8.9	36.6±8.8	37.2±8.6
Median (range)	38.0 (17–55)	36.0 (18–55)	37.0 (18–55)
Female sex — no. (%)	295 (68.8)	296 (69.6)	298 (71.3)
Disease and treatment history			
Time from first MS symptom to randomization — yr			
Mean	8.4±6.9	8.0±6.6	8.1±6.4
Median (range)	6.9 (0–37)	6.6 (0–35)	7.0 (0–32)
Relapses — no.			
Within previous yr			
Mean	1.5±0.8	1.5±0.8	1.4±0.7
Median (range)	1.0 (0–6)	1.0 (0–5)	1.0 (0–6)
Within previous 2 yr			
Mean	2.1±1.3	2.1±1.1	2.2±1.2
Median (range)	2.0 (1–10)	2.0 (1–11)	2.0 (1–10)
EDSS score†			
Mean	2.4±1.4	2.3±1.3	2.5±1.3
Median (range)	2.0 (0–5.5)	2.0 (0–5.5)	2.0 (0–5.5)
No history of disease-modifying treatment — no. (%)	259 (60.4)	244 (57.4)	249 (59.6)
Features on MRI‡			
Absence of gadolinium-enhancing lesions — no. (%)	257 (60.6)	263 (62.0)	262 (63.0)
No. of gadolinium-enhancing lesions on T_1-weighted images			
Mean	1.8±4.7	1.6±5.6	1.3±2.9
Median (range)	0 (0–50)	0 (0–84)	0 (0–26)
Volume of lesions on T_2-weighted images — mm^3			
Mean	6829±8491	6128±7623	6162±7085
Median (range)	3557 (0–47,734)	3303 (0–47,148)	3416 (0–37,148)
Volume of hypointense lesions on T_1-weighted images — mm^3			
Mean	2114±3220	1898±2854	1962±3131
Median (range)	860 (0–25,886)	814 (0–22,378)	811 (0–20,956)
Normalized brain volume — ml			
Mean	1511±86	1521±83	1512±85
Median (range)	1515 (1217–1764)	1529 (1144–1734)	1515 (1230–1723)

* Plus–minus values are means ±SD. There were no significant between-group differences at baseline for any characteristic. MS denotes multiple sclerosis.
† The Expanded Disability Status Scale (EDSS) ranges from 0 to 10, with higher scores indicating greater disability.
‡ MRI data were available for 424 patients in each of the fingolimod groups and for 416 patients in the placebo group. The means and medians were calculated on the basis of all images, not just those showing lesions.

Table 2. Clinical and MRI End Points, According to Study Group.*

End Point	Fingolimod		Placebo (N=418)	P Value	
	1.25 mg (N=429)	0.5 mg (N=425)		Fingolimod, 1.25 mg, vs. Placebo	Fingolimod, 0.5 mg, vs. Placebo
Primary end point					
Annualized relapse rate over 24 mo (95% CI)†‡	0.16 (0.13 to 0.19)	0.18 (0.15 to 0.22)	0.40 (0.34 to 0.47)	<0.001	<0.001
Relapse-related secondary end points					
Absence of relapse during the 24-mo period§					
Percent (95% CI)¶	74.7±2.2 (70.4 to 78.9)	70.4±2.3 (66.0 to 74.8)	45.6±2.5 (40.7 to 50.6)	<0.001	<0.001
Hazard ratio for fingolimod vs. placebo (95% CI)‖	0.38 (0.30 to 0.48)	0.48 (0.39 to 0.61)		<0.001	<0.001
Disability-related secondary end points					
Key secondary end point: absence of disability progression, confirmed after 3 mo, during the 24-mo period§					
Percent (95% CI)¶	83.4±1.9 (79.7 to 87.1)	82.3±1. 9 (78.6 to 86.1)	75.9±2.2 (71.7 to 80.2)	0.01	0.03
Hazard ratio for fingolimod vs. placebo (95% CI)**	0.68 (0.50 to 0.93)	0.70 (0.52 to 0.96)		0.02	0.02
Absence of disability progression, confirmed after 6 mo, during the 24-mo period§					
Percent (95% CI)¶	88.5±1.6 (85.3 to 91.6)	87.5±1.6 (84.3 to 90.7)	81.0±2.0 (77.1 to 84.9)	0.004	0.01
Hazard ratio for fingolimod vs. placebo (95% CI)**	0.60 (0.41 to 0.86)	0.63 (0.44 to 0.90)		0.006	0.01
EDSS score at 24 mo					
Mean††	–0.03±0.88	0.00±0.88	0.13±0.94	0.002	0.002
Median (range)	0.0 (–3.0 to 4.0)	0.0 (–3.0 to 3.5)	0.0 (–3.0 to 3.5)		
MSFC z score at 24 mo					
Mean††	0.01±0.40	0.03±0.39	–0.06±0.57	0.02	0.01
Median (range)	0.05 (–2.4 to 1.3)	0.07 (–2.1 to 1.2)	–0.01 (–3.8 to 5.5)		
MRI-related secondary end points§§					
Measures of inflammatory activity or scar formation					
No. of gadolinium-enhancing lesions at 24 mo¶¶					
No. of patients with data	343	369	332		
Mean‖‖	0.2±1.1	0.2±0.8	1.1±2.4	<0.001	<0.001
Median (range)	0.0 (0–11)	0.0 (0–8)	0.0 (0–21)		
Absence of gadolinium-enhancing lesions at 24 mo — no./total no. (%)¶¶‖‖	308/343 (89.8)	331/369 (89.7)	216/332 (65.1)	<0.001	<0.001

No. of new or enlarged lesions on T_2-weighted images, baseline to 24 mo***					
No. of patients with data	337	370	339		
Mean†††	2.5±5.5	2.5±7.2	9.8±13.2	<0.001	<0.001
Median (range)	0.0 (0 to 41)	0.0 (0 to 107)	5.0 (0 to 99)		
Absence of new or enlarged T_2-weighted lesions at 24 mo — no./total no. (%)***‡‡‡	175/337 (51.9)	187/370 (50.5)	72/339 (21.2)	<0.001	<0.001
Change in lesion volume on T_2-weighted images, baseline to 24 mo — %					
No. of patients with data	343	368	339		
Mean§§§	1.6±30.7	10.6±103.5	33.8±106.9	<0.001	<0.001
Median (range)	−3.10 (−68.2 to 221.5)	−1.69 (−100.0 to 1828.5)	8.61 (−84.5 to 1378.7)		
Measures of tissue damage or loss					
Change in volume of hypointense lesions on T_1-weighted images, baseline to 24 mo — %					
No. of patients with data	317	346	305		
Mean§§§	12.2±85.5	8.8±76.3	50.7±388.3	0.02	0.01
Median (range)	−0.20 (−100.0 to 888.4)	0.00 (−100.0 to 1037.1)	1.59 (−100.0 to 5285.3)		
Change in brain volume, baseline to 6 mo — %					
No. of patients with data	384	395	383		
Mean¶¶¶	−0.21±0.86	−0.22±0.81	−0.34±0.73	0.003	0.006
Median (range)	−0.12 (−4.71 to 3.37)	−0.14 (−5.62 to 2.25)	−0.29 (−4.02 to 2.57)		
Change in brain volume, baseline to 12 mo — %					
No. of patients with data	371	383	358		
Mean¶¶¶	−0.44±1.08	−0.50±1.05	−0.65±1.05	0.001	0.03
Median (range)	−0.30 (−4.91 to 4.34)	−0.38 (−8.11 to 2.40)	−0.56 (−3.89 to 2.78)		
Change in brain volume, 12 to 24 mo — %					
No. of patients with data	327	356	329		
Mean¶¶¶	−0.42±0.83	−0.37±0.81	−0.67±1.07	0.002	<0.001
Median (range)	−0.38 (−5.40 to 2.24)	−0.34 (−6.24 to 1.90)	−0.57 (−5.60 to 2.43)		

Change in brain volume, baseline to 24 mo					
No. of patients with data	334	357	331		
Mean¶¶¶	−0.89±1.39	−0.84±1.31	−1.31±1.50	<0.001	<0.001
Median (range)	−0.70 (−6.33 to 3.04)	−0.67 (−13.50 to 2.16)	−0.98 (−7.58 to 2.38)		

* Plus–minus values are means ±SD except where otherwise noted. All P values are two-sided. MSFC denotes Multiple Sclerosis Functional Composite (a quantitative measure of impairment in ambulation, upper-extremity function, and cognitive function), expressed as z scores, with higher scores indicating improvement.

† Data used in analyses were confirmed cases of relapse.

‡ P values were calculated with the use of a negative-binomial regression model with adjustment for study group, country, number of relapses within 2 years before the baseline value was measured, and the Expanded Disability Status Scale (EDSS) score (which ranges from 0 to 10, with higher scores indicating greater disability) at baseline.

§ Plus–minus values are means ±SE. Data regarding absence of relapse and absence of confirmed disability progression during the 24-mo period are based on Kaplan–Meier estimates.

¶ Plus–minus values are means ±SE. P values were calculated with the use of a log-rank test including data from baseline through 24 months.

‖ P values were calculated with the use of the Cox proportional-hazards model with adjustment for study group, country, number of relapses within 2 years before the baseline value was measured, and the EDSS score at baseline.

** P values were calculated with the use of the Cox proportional-hazards model with adjustment for study group, country, the EDSS score at baseline, and age.

†† P values were calculated with the use of analysis of covariance on ranks with adjustment for study group, country, baseline value of the given end point, and age.

‡‡ The MRI-related secondary end points presented here are descriptive measures of inflammatory activity or scar formation and measures of tissue damage or loss[26] rather than outputs of the analysis models.

§§ Any data regarding gadolinium-enhancing lesions obtained within 30 days after corticosteroid treatment for a relapse of multiple sclerosis were excluded from the analysis.

¶¶ P values were calculated with the use of analysis of covariance on ranks with adjustment for study group, country, and number of lesions at baseline.

‖‖ P values were calculated with the use of a logistic-regression model with adjustment for study group, country, and number of lesions at baseline.

*** For each patient, the number of new or enlarged T_2-hyperintense lesions was counted from baseline through 24 months by summing the count for the first 12 months and the count for the second 12 months.

††† P values were calculated with the use of a negative-binomial regression model with adjustment for study group and country.

‡‡‡ P values were calculated with the use of a logistic-regression model with adjustment for study group and country.

§§§ P values were calculated with the use of analysis of covariance on ranks with adjustment for study group, country, and lesion volume at baseline.

¶¶¶ P values were calculated with the use of analysis of covariance on ranks with adjustment for study group, country, and normalized brain volume at baseline.

at a dose of 1.25 mg (occurring in 14.2% of patients) than with fingolimod at a dose of 0.5 mg (occurring in 7.5%) or with placebo (occurring in 7.7%). Serious adverse events were reported for 10.1% of patients receiving 0.5 mg of fingolimod, 11.9% of those receiving 1.25 mg of fingolimod, and 13.4% of those receiving placebo. The most common serious adverse events, each reported for eight patients, were bradycardia, multiple sclerosis relapse, and basal-cell carcinoma. All other serious adverse events occurred in four or fewer patients (<1%) in any study group. The seven episodes of bradycardia in the two fingolimod groups (four in the 0.5-mg group and three in the 1.25-mg group) were reported during the monitoring period after administration of the first dose. Six of these events were asymptomatic; the patients continued to receive fingolimod and the episodes were reported as serious adverse events because the protocol-defined discharge criteria for the first-dose monitoring period were not met.

Three deaths occurred during the study, two with placebo and one with 1.25 mg of fingolimod. The causes of death in the placebo group were pulmonary embolism and a traffic accident, and the cause in the fingolimod group was suicide.

Infections

The overall incidence of infection was similar in the fingolimod and placebo groups (69 to 72%); serious infections occurred in 1.6 to 2.6% of patients. Urinary tract infection was the only serious infection reported in more than one patient (reported in two patients in the group receiving 0.5 mg of fingolimod). Herpesvirus infections were reported in similar proportions of patients across the three study groups (Table 3). Of these infections, herpes zoster was reported in seven patients receiving 0.5 mg of fingolimod, three receiving 1.25 mg of fingolimod, and four receiving placebo. Two cases of herpesvirus infection were classified as serious adverse events: one case of genital herpes (in a patient receiving 1.25 mg of fingolimod) and one case of herpes simplex labialis (in a patient receiving 0.5 mg of fingolimod).

Lower respiratory tract infections (including bronchitis and pneumonia) were more common with fingolimod than with placebo (occurring in 41 patients [9.6%] receiving 0.5 mg of fingolimod and 49 patients [11.4%] receiving 1.25 mg of fingolimod vs. 25 patients [6.0%] receiving placebo).

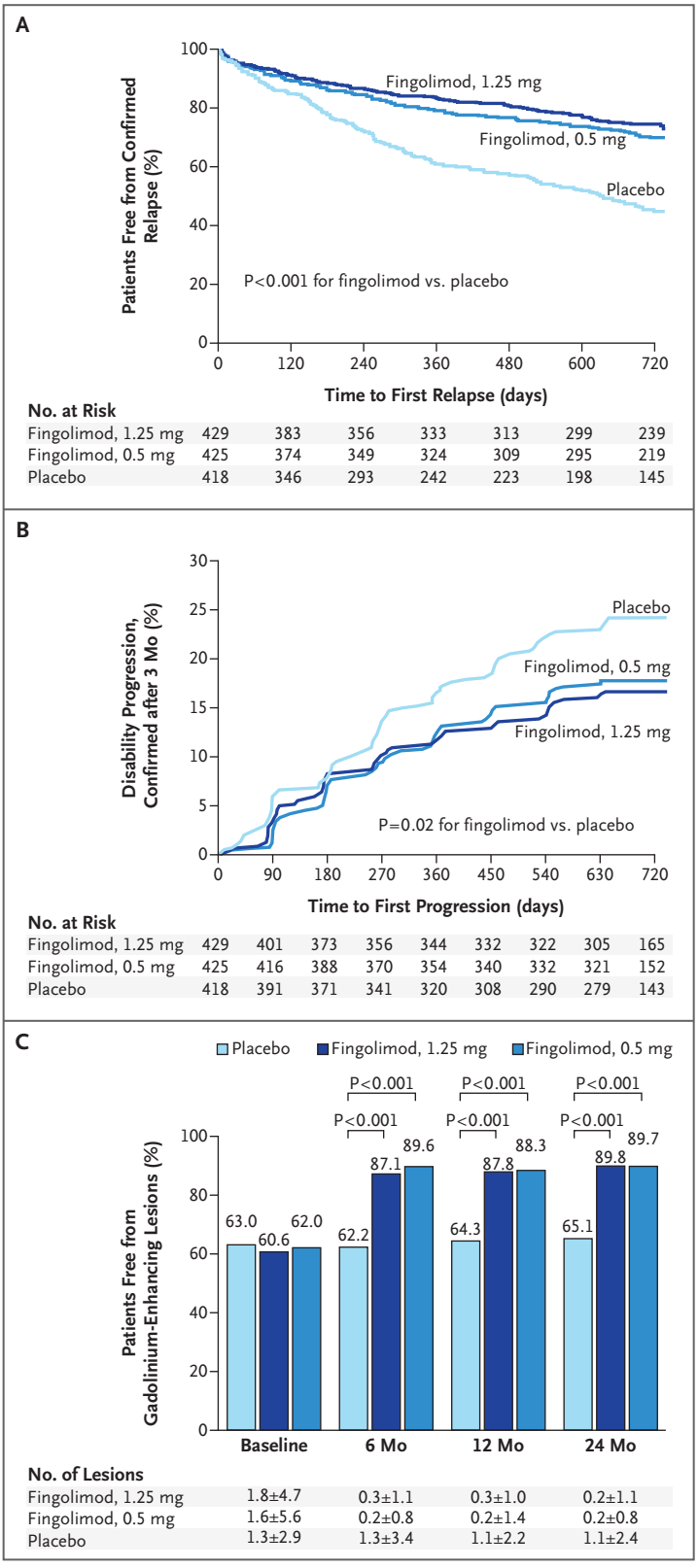

Figure 2. Study End Points, According to Study Group.

Panel A shows Kaplan–Meier estimates for the time to a first relapse, and Panel B shows Kaplan–Meier estimates for the time to disability progression, confirmed after 3 months, as measured with the Expanded Disability Status Scale (EDSS). Panel C shows the proportions of patients free from gadolinium-enhancing lesions and the mean (±SD) number of gadolinium-enhancing lesions at baseline and at 6, 12, and 24 months. Data on gadolinium-enhancing lesions were available for 416 patients assigned to receive placebo, 424 assigned to receive 1.25 mg of fingolimod, and 424 assigned to receive 0.5 mg of fingolimod, respectively, at baseline; 373, 388, and 403, respectively, at 6 months; 356, 376, and 394, respectively, at 12 months; and 332, 343, and 369, respectively, at 24 months. The P values for the proportions were obtained with the use of a logistic-regression model, with adjustment for study group, country, and number of lesions at baseline.

Cardiovascular Events

Transient, dose-related decreases in the heart rate occurred after the first dose of fingolimod was administered, a finding that is consistent with previous clinical experience.[13,15,24,27] Heart-rate decreases started 2 hours after receipt of the first dose, reaching the nadir after 4 to 5 hours, with attenuation beginning at 6 hours. The maximal reduction in the mean resting pulse rate, as compared with the baseline value, was 8 beats per minute 5 hours after the first dose of 0.5 mg of fingolimod and 10 beats per minute 4 hours after the first dose of 1.25 mg of fingolimod. Bradycardia (including the seven cases classified as serious adverse events) was reported in 9 patients receiving 0.5 mg of fingolimod, 14 receiving 1.25 mg of fingolimod, and 3 receiving placebo (Table 3). The majority of these events in the fingolimod groups occurred during the monitoring period after the first dose was administered (in 8 and 12 patients receiving 0.5 mg and 1.25 mg of fingolimod, respectively). Of these, six events were symptomatic (characterized by dizziness, chest discomfort, or palpitations) and all resolved with 24 hours; two patients received treatment for bradycardia.

First- and second-degree atrioventricular block was infrequently reported as an adverse event (Table 3). However, electrocardiography performed on day 1 revealed first-degree atrioventricular block in 20 patients receiving 0.5 mg of fingolimod, in 37 receiving 1.25 mg of fingolimod, and in 6 receiving placebo. Second-degree atrioven-

tricular block (also known as Mobitz I periodicity) was identified on electrocardiography on day 1 in one patient receiving 0.5 mg of fingolimod and in four patients receiving 1.25 mg of fingolimod. Second-degree atrioventricular block was symptomatic in one patient (in the 1.25-mg group), who had shortness of breath and palpitations (Table 3). No clinically notable effect on heart rate or atrioventricular conduction was seen with continued use of fingolimod.

Starting during month 2, the mean systolic and diastolic blood pressures obtained while the patient was seated increased from the baseline values; at month 24, they had increased by 1.9 and 0.7 mm Hg, respectively, with 0.5 mg of fingolimod and by 3.6 and 2.1 mm Hg, respectively, with 1.25 mg of fingolimod and had decreased by 0.4 and 0.5 mm Hg, respectively, in the placebo group.

Ophthalmic Events

Macular edema was diagnosed in seven patients, all of whom were receiving 1.25 mg of fingolimod. Three of these events were reported as serious adverse events (Table 3). Five of these seven cases of macular edema occurred within 3 months after the start of therapy. Six cases resolved within 1 to 6 months after treatment was discontinued. Mean visual acuity and central foveal thickness remained stable in all patients throughout the study.

Neoplasms

Malignant neoplasms were reported in 4 patients receiving 0.5 mg of fingolimod, 4 receiving 1.25 mg of fingolimod, and 10 receiving placebo (Table 3). All 11 skin cancers (basal-cell carcinoma, malignant melanoma, or Bowen's disease) that occurred (3 cases with 1.25-mg fingolimod, 4 with 0.5-mg fingolimod, and 4 with placebo) were removed successfully.

Laboratory Abnormalities

At 1 month, peripheral-blood lymphocyte counts were reduced from the baseline counts by an average of 73% with 0.5 mg of fingolimod and 76% with 1.25 mg of fingolimod, remaining stable thereafter (see the Supplementary Appendix). These were not reported as adverse events by the investigators, who remained unaware of the actual values unless they dropped to less than 0.2×10^9 per liter. Increases in the alanine aminotransferase level to three times the upper limit of the normal range or more were more frequent in the fingolimod groups (reported in 8.5% of patients in the 0.5-mg group and 12.5% in the 1.25-mg group) than in the placebo group (1.7%) and occurred predominantly in men. One patient receiving 0.5 mg of fingolimod had an increase in the alanine aminotransferase level to more than 10 times the upper limit of the normal range. Elevated liver-enzyme levels returned to normal in all patients, even in the few who continued the study treatment. In all three groups, bilirubin levels remained stable, with no clinically relevant changes during the study.

DISCUSSION

This 2-year study showed that as compared with placebo, both doses of fingolimod tested reduced the annualized relapse rate. Disability progression was also significantly reduced in patients receiving fingolimod as compared with those receiving placebo. These clinical findings are supported by the results regarding the MRI end points and are in line with the results of a 6-month, placebo-controlled, phase 2 study[13] and a 1-year, phase 3 study comparing fingolimod with an active drug (intramuscular interferon beta-1a) (TRANSFORMS).[15]

The 30% reduction in the rate of reduction of brain volume in this study — detected as early as 6 months after initiation of the study drug and also seen over a 12-month period in TRANSFORMS[15] — is an interesting corollary to the clinical findings. It remains to be established whether this effect is due to the reduction in inflammatory activity or reflects direct interactions between the drug and sphingosine-1-phosphate receptors on neural cells,[6,7,10] as suggested by studies in animals and by in vitro observations.[6-12]

This study also provides important 2-year, placebo-controlled information about the safety of fingolimod. As medications used to treat multiple sclerosis become increasingly potent, attention to safety findings is paramount. Possible concerns include infections, cardiovascular effects, macular edema, and elevated liver-enzyme levels. The safety profile warrants further longer-term assessment.

As expected on the basis of its mechanism of action, fingolimod treatment led to a reduction in circulating lymphocytes of approximately 70%

Table 3. Adverse Events in the Safety Population, According to Study Group.

Event	Fingolimod		Placebo (N=418)
	1.25 mg (N=429)	0.5 mg (N=425)	
	no. of patients (%)		
All events			
At least one adverse event	404 (94.2)	401 (94.4)	387 (92.6)
Any adverse event leading to discontinuation of study drug*	61 (14.2)	32 (7.5)	32 (7.7)
Any serious adverse event	51 (11.9)	43 (10.1)	56 (13.4)
Death	1 (0.2)	0	2 (0.5)
Frequent or special-interest adverse events†			
Infections			
Upper respiratory tract infection	206 (48.0)	212 (49.9)	211 (50.5)
Nasopharyngitis	112 (26.1)	115 (27.1)	115 (27.5)
Sinusitis	27 (6.3)	28 (6.6)	19 (4.5)
Pharyngitis	25 (5.8)	27 (6.4)	24 (5.7)
Rhinitis	18 (4.2)	25 (5.9)	25 (6.0)
Influenza virus infection	40 (9.3)	55 (12.9)	41 (9.8)
Lower respiratory tract or lung infection	49 (11.4)	41 (9.6)	25 (6.0)
Bronchitis	39 (9.1)	34 (8.0)	15 (3.6)
Pneumonia	8 (1.9)	4 (0.9)	3 (0.7)
Herpesvirus infection‡	25 (5.8)	37 (8.7)	33 (7.9)
Urinary tract infection	21 (4.9)	34 (8.0)	47 (11.2)
Nervous system disorders			
Headache	114 (26.6)	107 (25.2)	96 (23.0)
Dizziness	30 (7.0)	31 (7.3)	23 (5.5)
Paresthesia	17 (4.0)	23 (5.4)	18 (4.3)
Abnormal laboratory liver-function test§	80 (18.6)	67 (15.8)	21 (5.0)
Fatigue	47 (11.0)	48 (11.3)	45 (10.8)
Musculoskeletal disorders			
Back pain	45 (10.5)	50 (11.8)	29 (6.9)
Arthralgia	27 (6.3)	30 (7.1)	33 (7.9)
Pain in extremity	24 (5.6)	28 (6.6)	28 (6.7)
Gastrointestinal disorders			
Diarrhea	40 (9.3)	50 (11.8)	31 (7.4)
Nausea	38 (8.9)	38 (8.9)	36 (8.6)
Respiratory disorders			
Cough	37 (8.6)	43 (10.1)	34 (8.1)
Dyspnea	23 (5.4)	30 (7.1)	19 (4.5)
Oropharyngeal pain	17 (4.0)	29 (6.8)	29 (6.9)
Blood and lymphatic system disorders			
Leukopenia	27 (6.3)	12 (2.8)	1 (0.2)
Lymphopenia	23 (5.4)	15 (3.5)	2 (0.5)
Cardiovascular disorders			
Hypertension	27 (6.3)	26 (6.1)	16 (3.8)
Bradycardia, bradyarrhythmia, or sinus bradycardia	14 (3.3)	9 (2.1)	3 (0.7)
Atrioventricular block			
First degree	5 (1.2)	2 (0.5)	2 (0.5)
Second degree	1 (0.2)	0	1 (0.2)

Table 3. (Continued.)

Event	Fingolimod		Placebo (N=418)
	1.25 mg (N=429)	0.5 mg (N=425)	
	no. of patients (%)		
Psychiatric disorders			
Depression	26 (6.1)	33 (7.8)	28 (6.7)
Insomnia	16 (3.7)	21 (4.9)	25 (6.0)
Hypercholesterolemia	26 (6.1)	24 (5.6)	26 (6.2)
Weight increase	14 (3.3)	14 (3.3)	22 (5.3)
Vertigo	18 (4.2)	18 (4.2)	21 (5.0)
Macular edema	7 (1.6)	0	0
Serious adverse events¶			
Cardiovascular disorders			
Bradycardia	3 (0.7)	4 (0.9)	1 (0.2)
Myocardial infarction	0	0	2 (0.5)
Neoplasms			
Basal-cell carcinoma	1 (0.2)	4 (0.9)	3 (0.7)
Breast cancer	1 (0.2)	0	3 (0.7)
Malignant melanoma	1 (0.2)	0	1 (0.2)
Bowen's disease	1 (0.2)	0	0
Cervical carcinoma, stage 0	0	0	1 (0.2)
Endometrial cancer	0	0	1 (0.2)
Prostate cancer	0	0	1 (0.2)
Nervous system disorders			
MS relapse‖	3 (0.7)	4 (0.9)	1 (0.2)
Epilepsy	2 (0.5)	0	0
Headache	2 (0.5)	0	0
General disorders			
Chest pain	0	4 (0.9)	2 (0.5)
Macular edema	3 (0.7)	0	0
Laboratory evaluation			
Abnormal liver-function test	2 (0.5)	0	1 (0.2)
Lymphopenia	2 (0.5)	0	0
Depression	2 (0.5)	0	1 (0.2)
Musculoskeletal disorders			
Back pain	0	2 (0.5)	1 (0.2)
Intervertebral disk protrusion	0	0	2 (0.5)
Abortion	0	0	3 (0.7)
Urinary tract infection	0	2 (0.5)	0

* "Any adverse event leading to discontinuation of the study drug" includes events occurring in patients whose primary or secondary reason for discontinuing the study drug was an adverse event (including abnormal laboratory findings).
† "Frequent adverse events" includes those reported in 5% or more of patients in any group.
‡ The terms used to report herpesvirus infection included oral herpes, herpesvirus infection, herpes simplex virus infection, herpes zoster, genital herpes, and herpes dermatitis.
§ The terms used to report an abnormal laboratory liver-function test included increased levels of alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, hepatic enzyme, and aminotransferases, and abnormal liver-function tests or γ-glutamyltransferase levels.
¶ "Serious adverse events" includes those reported in two or more patients in any group or of special interest.
‖ "MS relapse" includes both events related to the worsening of multiple sclerosis (MS) and MS relapses. See the Supplementary Appendix for further details.

in the present study. The overall incidence of infection was similar across the three study groups, with the exception of lower respiratory tract infections, which were more common with fingolimod than with placebo. Although similar proportions of patients in the three groups had herpesvirus infections, reactivation of latent herpes remains a potential risk with immunomodulatory therapy; two fatal herpes infections occurred in TRANSFORMS with the 1.25-mg dose of fingolimod.[15]

Cardiovascular effects of fingolimod included slowing of the heart rate and atrioventricular conduction block at the time of the first dose. These effects appear to be dose-dependent and specifically related to the binding of the drug to sphingosine-1-phosphate receptors in cardiac tissue.[28] Interactions with sphingosine-1-phosphate receptors in smooth muscle may account for the mild increase in blood pressure seen during long-term treatment. The long-term relevance of this finding is unclear.

Fingolimod was infrequently associated with macular edema, which resolved with discontinuation of the drug. The frequency of this complication and possible implications during long-term use are not known.

Elevations in liver-enzyme levels were common findings in this study and in earlier studies.[13,24] These elevated values resolved after fingolimod was discontinued.[13,15,24]

Our findings do not suggest an increased risk of cancer with the use of fingolimod. However, further long-term observation is necessary, since the risk of cancer is potentially increased by the use of any immunomodulatory agent.

In conclusion, oral fingolimod as compared with placebo had superior efficacy in this 24-month study involving patients with relapsing–remitting multiple sclerosis. Rates of relapse, progression of clinical disability, and MRI evidence of inflammatory lesion activity and tissue destruction were all significantly reduced with the use of fingolimod. The two doses of fingolimod had similar efficacy, and adverse events may be less frequent with the 0.5-mg dose than with the 1.25-mg dose. Thorough observation and long-term follow-up are necessary for a more informed assessment of the benefits and risks of this new treatment option for relapsing multiple sclerosis.

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