ORIGINAL ARTICLE

# Oral Fingolimod or Intramuscular Interferon for Relapsing Multiple Sclerosis

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## ABSTRACT

### BACKGROUND

Fingolimod (FTY720), a sphingosine-1-phosphate–receptor modulator that prevents lymphocyte egress from lymph nodes, showed clinical efficacy and improvement on imaging in a phase 2 study involving patients with multiple sclerosis.

### METHODS

In this 12-month, double-blind, double-dummy study, we randomly assigned 1292 patients with relapsing–remitting multiple sclerosis who had a recent history of at least one relapse to receive either oral fingolimod at a daily dose of either 1.25 or 0.5 mg or intramuscular interferon beta-1a (an established therapy for multiple sclerosis) at a weekly dose of 30 $\mu$g. The primary end point was the annualized relapse rate. Key secondary end points were the number of new or enlarged lesions on $T_2$-weighted magnetic resonance imaging (MRI) scans at 12 months and progression of disability that was sustained for at least 3 months.

### RESULTS

A total of 1153 patients (89%) completed the study. The annualized relapse rate was significantly lower in both groups receiving fingolimod — 0.20 (95% confidence interval [CI], 0.16 to 0.26) in the 1.25-mg group and 0.16 (95% CI, 0.12 to 0.21) in the 0.5-mg group — than in the interferon group (0.33; 95% CI, 0.26 to 0.42; P<0.001 for both comparisons). MRI findings supported the primary results. No significant differences were seen among the study groups with respect to progression of disability. Two fatal infections occurred in the group that received the 1.25-mg dose of fingolimod: disseminated primary varicella zoster and herpes simplex encephalitis. Other adverse events among patients receiving fingolimod were nonfatal herpesvirus infections, bradycardia and atrioventricular block, hypertension, macular edema, skin cancer, and elevated liver-enzyme levels.

### CONCLUSIONS

This trial showed the superior efficacy of oral fingolimod with respect to relapse rates and MRI outcomes in patients with multiple sclerosis, as compared with intramuscular interferon beta-1a. Longer studies are needed to assess the safety and efficacy of treatment beyond 1 year. (ClinicalTrials.gov number, NCT00340834.)

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*The members of the Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing–Remitting Multiple Sclerosis (TRANSFORMS) study group are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org.

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Oral fingolimod (FTY720) is a sphingosine-1-phosphate–receptor modulator. After phosphorylation, fingolimod acts as a functional antagonist of the sphingosine-1-phosphate type 1 receptor, inducing receptor internalization and rendering T and B cells insensitive to a signal necessary for egress from secondary lymphoid tissues.[1,2] The resulting redistribution to lymph nodes reduces recirculation of autoaggressive lymphocytes to the central nervous system.[3-5] Also, fingolimod is lipophilic, readily crosses the blood–brain barrier, and is phosphorylated within the central nervous system.[6] Through interaction with sphingosine-1-phosphate receptors on neural cells, fingolimod may have neuroprotective or reparative effects.[6-9]

Fingolimod effectively treats experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis.[1,10,11] In a 6-month, phase 2 study involving patients with relapsing multiple sclerosis,[12] daily oral fingolimod at a dose of 5.0 or 1.25 mg significantly reduced the number of gadolinium-enhancing lesions seen on magnetic resonance imaging (MRI) and the relapse rate, as compared with placebo. In an extension study, clinical and MRI benefits were maintained for up to 5 years, and no new safety issues were identified.[13,14]

In this 12-month, phase 3, multicenter, randomized, double-blind, double-dummy, parallel-group study, called the Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing–Remitting Multiple Sclerosis (TRANSFORMS), we compared the efficacy and safety of fingolimod with that of intramuscular interferon beta-1a, an established therapy for multiple sclerosis.

## Methods

### Patients

Patients were eligible to participate in the study if they were between 18 and 55 years of age, had received a diagnosis of multiple sclerosis that met the revised McDonald criteria,[15] had disease with a relapsing–remitting course,[16] had had at least one documented relapse during the previous year or at least two documented relapses during the previous 2 years, and had a score of 0 to 5.5 on the Expanded Disability Status Scale (EDSS) (ranging from 0 to 10, with higher scores indicating a greater degree of disability).[17] Other exclusion criteria were a documented relapse or corticosteroid treatment within 30 days before randomization, active infection, macular edema, immunosuppression (either drug- or disease-induced), and clinically significant coexisting systemic disease. Previous recent therapy with either any type of interferon beta or glatiramer acetate was not a criterion for exclusion.

The study was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice[18] and the principles of the Declaration of Helsinki.[19] The protocol was approved by the institutional review board at each study site. All patients provided written informed consent before any study-related procedure was performed.

### Study Oversight

A steering committee consisting of academic investigators collaborated with the sponsor (Novartis Pharma) to design the study and monitor its conduct. Data were collected by the site investigators and analyzed by the sponsor. All the authors had access to all data, participated in all analyses and their interpretation, wrote the manuscript, and decided to submit the manuscript for publication. The authors attest to the completeness and accuracy of the data and the analyses. During the study, the investigators, participating institutions, and sponsor agreed to maintain confidentiality of the data.

### Study Design

Patients were randomly assigned to 12 months of treatment with oral fingolimod, at a daily dose of either 1.25 or 0.5 mg, or intramuscular interferon beta-1a (Avonex, Biogen Idec), at a weekly dose of 30 $\mu$g. Randomization was performed centrally in blocks of six within each site and was stratified according to site. Study-group assignments were performed with the use of an interactive voice-response system. At each site, a treating neurologist supervised medical management. A specially trained and certified[20] examining neurologist determined EDSS scores at scheduled and unscheduled visits. The examining neurologist or a trained technician calculated Multiple Sclerosis Functional Composite (MSFC) scores, which included the average of 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. Each of these scores was converted to a z score on the basis of the combined study population at baseline as the reference population, with higher scores indicating improvement.[21]


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During the trial, patients, study personnel, MRI evaluators, steering-committee members, and the study statistician were unaware of study-group assignments and leukocyte counts. Capsules, syringes, and packaging materials for active and placebo treatments were indistinguishable. Patients were instructed to cover injection sites at visits and not to discuss adverse events with clinical evaluators. An independent physician monitored patients after the first dose of the oral study drug was administered and was instructed not to discuss heart-rate changes with patients or study personnel. Employees of the sponsor working independently of the study team monitored first-dose safety data. An independent data and safety monitoring board evaluated overall safety in the fingolimod phase 3 program. No interim efficacy analysis was performed.

### STUDY PROCEDURES

Safety assessments were conducted during screening, at baseline, and at months 1, 2, 3, 6, 9, and 12. EDSS scores were determined every 3 months, and MSFC scores every 6 months. Standardized MRI scans were obtained at screening and at 12 months and were analyzed centrally by the Image Analysis Center in Amsterdam.

Relapse was defined as new, worsening, or recurrent neurologic symptoms that occurred at least 30 days after the onset of a preceding relapse, that lasted at least 24 hours without fever or infection, and that were accompanied by an increase of at least half a point on the EDSS or an increase of at least one point in two functional-systems scores or of at least two points in one functional-system score (excluding changes in bowel or bladder function and cognition). Potential relapses triggered an unscheduled visit and were confirmed by the treating neurologist on the basis of blinded examination by the examining neurologist. Progression of disability was defined as a one-point increase in the EDSS score (or a half-point increase for patients with a baseline score ≥5.5) that was confirmed 3 months later in the absence of relapse. Additional methodologic details are available in the Supplementary Appendix, available with the full text of this article at NEJM.org.

### STUDY END POINTS

The primary efficacy end point was the annualized relapse rate, which was defined as the number of confirmed relapses during a 12-month period. The two key secondary end points were the number of new or enlarged hyperintense lesions on $T_2$-weighted MRI scans at 12 months and the time to confirmed disability progression.

### STATISTICAL ANALYSIS

We based our sample-size estimates on a phase 2 trial of fingolimod[12] and a phase 3 trial of interferon beta-1a,[22] which showed an annualized relapse rate of 0.33 for a 1.25-mg dose of fingolimod and of 0.55 for interferon beta-1a, a common standard deviation of 0.9, and 57 study-drug discontinuations per year per group. Using the Wilcoxon–Mann–Whitney rank-sum test, we estimated that an enrollment of 425 patients per study group would be needed to provide a power of 90% at a two-sided significance level of 0.05.

To control for type I errors, multiplicity adjustment was applied to testing for comparisons between fingolimod and interferon beta-1a in a hierarchical order, according to the dose of fingolimod, for the study end points. Each test was performed at a significance level of 0.05. However, the lower-rank testing was performed only when every higher-rank test indicated statistical significance.

The modified intention-to-treat cohort, which consisted of all patients who underwent randomization and received at least one dose of a study drug, was the primary focus for efficacy and safety analyses. The study was designed to test the null hypothesis that there would be no significant differences in the annualized relapse rate between either of the fingolimod groups and the interferon group with the use of a negative binomial regression model with adjustment for study group, country, number of relapses in the previous 2 years, and baseline EDSS score. These prespecified covariates were based on exploratory analyses of the phase 2 study data.[12] Heterogeneity in efficacy according to whether patients had undergone previous therapy was tested as a post hoc analysis with the use of the same negative binomial regression model, with the addition of the interaction term for therapy during the study and before baseline. Additional details concerning statistical methods are available in the Supplementary Appendix.

## RESULTS

### STUDY POPULATION

From May 2006 through September 2007, a total of 1292 patients underwent randomization at 172 clinical centers in 18 countries. Of these patients,

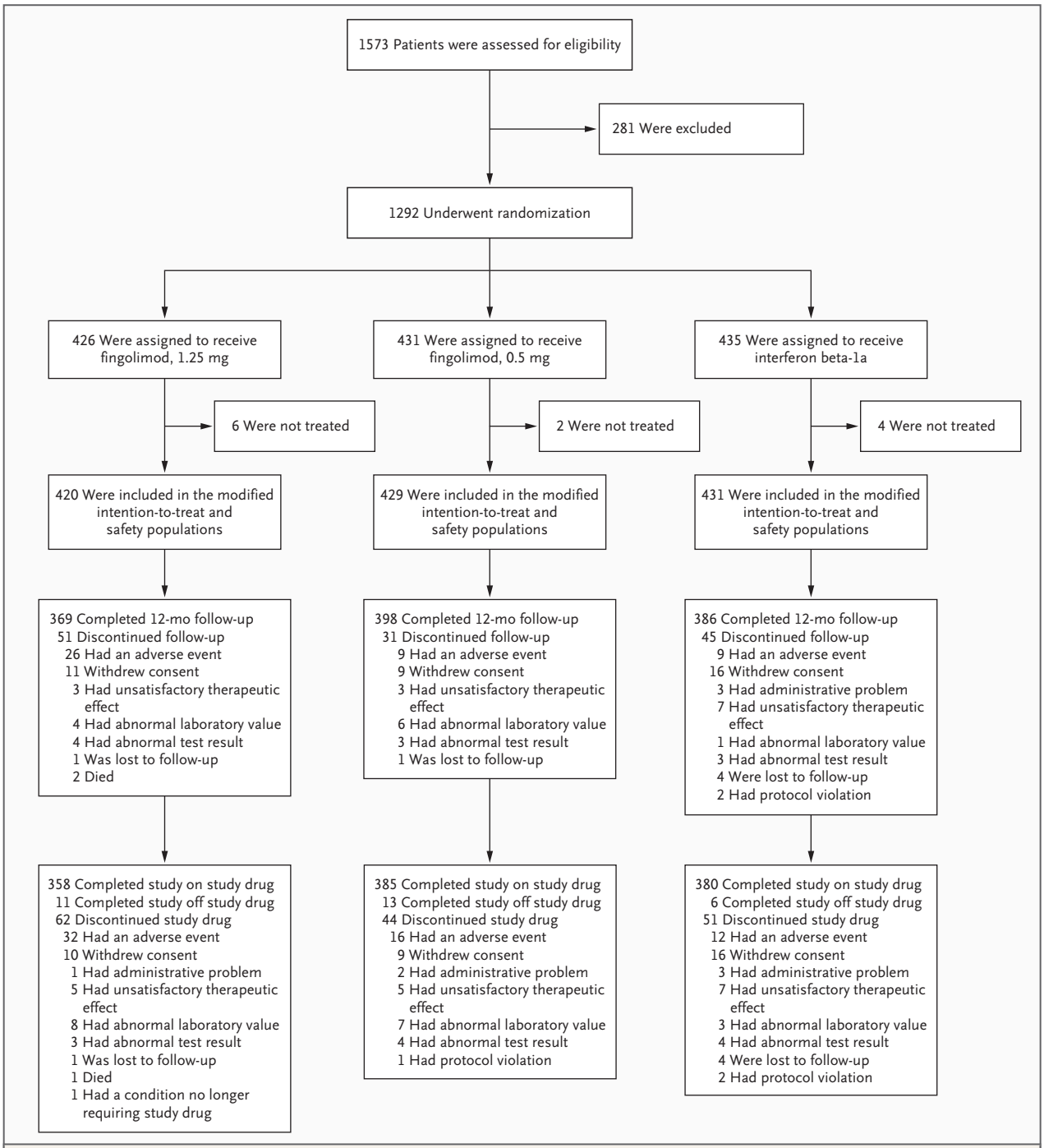


**Figure 1. Enrollment and Outcomes.**

The numbers of patients who discontinued a study drug include all those in the modified intention-to-treat population, regardless of whether they completed the 12-month follow-up.

12 were excluded before receiving any study drug or undergoing any safety or efficacy assessments because they did not meet eligibility criteria (Fig. 1). Baseline characteristics were similar across the study groups and were consistent with a population of patients with clinically active, relapsing–remitting multiple sclerosis (Table 1). In all, 1153 patients (89%) completed the study, and 1123 (87%)

**Table 1. Baseline Characteristics of the Patients.***

| Characteristic | Fingolimod | | Interferon Beta-1a (N=435) |
|---|---|---|---|
| | 1.25 mg (N=426) | 0.5 mg (N=431) | |
| **Demographic characteristics** | | | |
| Age — yr | | | |
| Mean | 35.8±8.4 | 36.7±8.8 | 36.0±8.3 |
| Median (range) | 36 (18–54) | 37 (18–55) | 36 (18–55) |
| Female sex — no. (%) | 293 (68.8) | 282 (65.4) | 295 (67.8) |
| White race — no. (%)† | 404 (94.8) | 404 (93.7) | 408 (93.8) |
| **Clinical characteristics** | | | |
| Interval from onset of symptoms to randomization — yr | | | |
| Mean | 7.3±6.0 | 7.5±6.2 | 7.4±6.3 |
| Median (range) | 6 (0–33) | 6 (0–34) | 6 (0–40) |
| Relapses in previous yr — no. | | | |
| Mean | 1.5±0.9 | 1.5±1.2 | 1.5±0.8 |
| Median (range) | 1 (0–7) | 1 (0–20) | 1 (0–6) |
| Relapses in previous 2 yr — no. | | | |
| Mean | 2.2±1.2 | 2.3±2.2 | 2.3±1.2 |
| Median (range) | 2 (1–8) | 2 (1–40) | 2 (1–12) |
| EDSS score‡ | | | |
| Mean | 2.21±1.31 | 2.24±1.33 | 2.19±1.26 |
| Median (range) | 2.0 (0–5.5) | 2.0 (0–5.5) | 2.0 (0–5.5) |
| **Treatment history§** | | | |
| Any therapy — no. (%) | 249 (58.5) | 238 (55.2) | 245 (56.3) |
| Any interferon beta | 209 (49.1) | 219 (50.8) | 207 (47.6) |
| Glatiramer acetate | 67 (15.7) | 57 (13.2) | 67 (15.4) |
| Natalizumab | 3 (0.7) | 4 (0.9) | 1 (0.2) |
| **MRI findings¶** | | | |
| Patients with no gadolinium-enhancing lesions on $T_1$-weighted images — no./total no. (%) | 270/412 (65.5) | 288/427 (67.4) | 268/425 (63.1) |
| No. of gadolinium-enhancing lesions on $T_1$-weighted images | | | |
| Mean | 1.49±4.77 | 0.98±2.81 | 1.06±2.80 |
| Median (range) | 0 (0–66) | 0 (0–29) | 0 (0–36) |
| Volume of lesions on $T_2$-weighted images — $mm^3$ | | | |
| Mean | 5085±5962 | 5170±6642 | 4924±5711 |
| Median (range) | 3096 (0–38,870) | 2382 (0–46,280) | 2901 (0–38,712) |
| Normalized brain volume — $cm^3$ | | | |
| Mean | 1526.2±76.4 | 1524.1±83.9 | 1526.7±77.9 |
| Median (range) | 1528 (1300–1794) | 1526 (1185–1862) | 1533 (1231–1762) |

* Plus–minus values are means ±SD. None of the between-group comparisons were significant.
† Race was self-reported.
‡ Scores on the Expanded Disability Status Scale (EDSS) range from 0 to 10, with higher scores indicating a greater degree of disability.
§ Patients may have received more than one treatment before study entry.
¶ All MRI findings were based on all images that could be evaluated.

**Table 2. Clinical and MRI Results at 12 Months.***

| End Point | Fingolimod | | Interferon Beta-1a (N=431) | P Value | |
|---|---|---|---|---|---|
| | 1.25 mg (N=420) | 0.5 mg (N=429) | | Fingolimod, 1.25 mg, vs. Interferon Beta-1a | Fingolimod, 0.5 mg, vs. Interferon Beta-1a |
| **Relapse** | | | | | |
| Annualized relapse rate (primary end point) — no. (95% CI) | 0.20 (0.16 to 0.26) | 0.16 (0.12 to 0.21) | 0.33 (0.26 to 0.42) | <0.001 | <0.001 |
| Rate for patients who had no previous disease-modifying therapy — no. (95% CI)† | 0.17 (0.11 to 0.25) | 0.15 (0.10 to 0.23) | 0.31 (0.22 to 0.41) | | |
| Rate for patients who had previous disease-modifying therapy — no. (95% CI) | 0.33 (0.26 to 0.42) | 0.26 (0.19 to 0.34) | 0.53 (0.43 to 0.65) | | |
| Patients with no confirmed relapse — % (95% CI)‡ | 79.8 (75.9 to 83.7) | 82.6 (79.0 to 86.3) | 69.3 (64.8 to 73.8) | <0.001 | <0.001 |
| Patients with confirmed relapse — no. (%) | | | | | |
| 0 relapse | 338 (80.5) | 354 (82.5) | 302 (70.1) | <0.001 | <0.001 |
| 1 relapse | 61 (14.5) | 63 (14.7) | 90 (20.9) | | |
| 2 relapses | 19 (4.5) | 11 (2.6) | 30 (7.0) | | |
| ≥3 relapses | 2 (0.5) | 1 (0.2) | 9 (2.1) | | |
| **MRI outcome§** | | | | | |
| New or enlarged lesions on $T_2$-weighted images — no. | | | | | |
| Mean | 1.5±2.7 | 1.7±3.9 | 2.6±5.8 | <0.001 | 0.004 |
| Median (range) | 1 (0 to 26) | 0 (0 to 38) | 1 (0 to 63) | | |
| Gadolinium-enhancing lesions on $T_1$-weighted images — no. | | | | | |
| Mean | 0.14±0.58 | 0.23±0.97 | 0.51±1.86 | <0.001 | <0.001 |
| Median (range) | 0 (0 to 6) | 0 (0 to 11) | 0 (0 to 24) | | |
| Patients with no new or enlarged lesions on $T_2$-weighted images — no./total no. (%) | 168/350 (48.0) | 204/372 (54.8) | 165/361 (45.7) | 0.37 | 0.01 |
| Patients with no gadolinium-enhancing lesions on $T_1$-weighted images — no./total no. (%) | 321/352 (91.2) | 337/374 (90.1) | 286/354 (80.8) | <0.001 | <0.001 |

| | | | | | |
|---|---|---|---|---|---|
| Volume of gadolinium-enhancing lesions on $T_1$-weighted images — $mm^3$ | | | | | |
| Mean | 19.54±109.10 | 22.61±111.59 | 50.68±198.16 | <0.001 | <0.001 |
| Median (range) | 0 (0 to 1442) | 0 (0 to 1359) | 0 (0 to 2238) | | |
| Change from baseline in volume of hyperintense lesions on $T_2$-weighted images — % | | | | | |
| Mean | 6.7±31.0 | 9.9±37.3 | 10.4±42.8 | 0.48 | 0.63 |
| Median (range) | 2.9 (–76.1 to 247.1) | 6.2 (–100.0 to 318.2) | 3.0 (–60.7 to 494.1) | | |
| Change from baseline in volume of hypointense lesions on $T_1$-weighted images — % | | | | | |
| Mean | 34.7±122.3 | 24.1±127.3 | 15.0±70.3 | 0.09 | 0.17 |
| Median (range) | 4.4 (–100.0 to 1291.8) | 3.2 (–100.0 to 2061.1) | 1.2 (–100.0 to 636.4) | | |
| Change from baseline in brain volume — % | | | | | |
| Mean | –0.30±0.65 | –0.31±0.65 | –0.45±0.73 | <0.001 | <0.001 |
| Median (range) | –0.20 (–2.90 to 2.20) | –0.20 (–3.70 to 2.00) | –0.40 (–3.40 to 2.60) | | |
| **Disability** | | | | | |
| Patients with no confirmed disability progression — % (95% CI)‡ | 93.3 (90.9 to 95.8) | 94.1 (91.8 to 96.3) | 92.1 (89.4 to 94.7) | 0.50 | 0.25 |
| Change from baseline in EDSS score¶ | | | | | |
| Mean | –0.11±0.90 | –0.08±0.79 | 0.01±0.78 | 0.02 | 0.06 |
| Median (range) | 0 (–3.0 to 5.0) | 0 (–3.0 to 2.5) | 0 (–2.0 to 3.0) | | |
| Change from baseline in MSFC z score‖ | | | | | |
| Mean | 0.08±0.46 | 0.04±0.42 | –0.03±0.48 | <0.001 | 0.02 |
| Median (range) | 0.06 (–1.90 to 3.60) | 0.20 (–2.10 to 4.70) | –0.01 (–5.30 to 1.70) | | |

* Plus–minus values are means ±SD. Data are for the modified intention-to-treat population, which consisted of all patients who underwent randomization and received at least one dose of a study drug.
† Among patients receiving fingolimod, P values for the interaction between therapy during the study period and before baseline, as compared with the interferon group, were 0.49 for the 1.25-mg group and 0.81 for the 0.5-mg group.
‡ Values are Kaplan–Meier estimates from the analysis of time to first relapse.
§ All MRI outcomes were based on all images that could be evaluated.
¶ Scores on the Expanded Disability Status Scale (EDSS) range from 0 to 10, with higher scores indicating a greater degree of disability.
‖ Scores on the Multiple Sclerosis Functional Composite (MSFC) are expressed as z scores, with higher scores indicating improvement in disability.

continued to receive the assigned study drug. A slightly greater proportion of patients assigned to fingolimod at a dose of 1.25 mg discontinued treatment or study participation because of adverse events, as compared with the other two groups. Other reasons for discontinuation were equally distributed among the study groups.

## EFFICACY

### *Relapse*

Table 2 summarizes the relapse rates, MRI outcomes, and results with respect to disability progression. There was a significantly greater reduction in the annualized relapse rates in both fingolimod groups than in the interferon group. Other relapse-related measures also significantly favored fingolimod, including the proportion of patients who were relapse-free, the proportion with multiple relapses, and the time to the first relapse (Fig. 2). There was no significant difference in the magnitude of the treatment effect between patients who had previously undergone disease treatment and those who had not.

### *MRI Outcomes*

Patients in the two fingolimod groups had significantly fewer new or enlarged hyperintense lesions on $T_2$-weighted images and gadolinium-enhancing lesions on $T_1$-weighted images at 12 months than did those in the interferon group. The mean percent reduction in brain volume from baseline to 12 months was significantly lower in the two fingolimod groups than in the interferon group. Changes in the volume of lesions on enhanced $T_2$- or $T_1$-weighted images at 12 months did not differ significantly among the study groups.

### *Disability*

Confirmed disability progression was infrequent in all the study groups. There were no significant differences in the time to the progression of disability or in the proportion of patients with confirmed progression among the study groups.

## ADVERSE EVENTS

### *Serious Events*

Adverse events were reported for similar proportions of patients in the three study groups, ranging from 86 to 92% (Table 3). Of these events, 87 to 90% were mild or moderate in severity. Serious adverse events and those leading to the discontinuation of a study drug were most frequent in the patients assigned to fingolimod at the 1.25-mg dose. The most common serious events in this group were bradycardia and atrioventricular block. All such events were observed after the first administration of fingolimod, and most were asymptomatic but were reported as serious adverse events because protocol-defined discharge criteria at 6 hours were not met, leading to mandatory hospitalization. All other serious adverse events occurred in fewer than four patients (<1%) in any study group.

There were two deaths during the trial, both in the group assigned to fingolimod at a dose of 1.25 mg. One of these deaths was caused by disseminated primary varicella zoster infection in a patient with no history of chicken pox and a negative baseline varicella zoster antibody titer who was exposed to a child with chicken pox during an 8-day course of corticosteroids (intravenous and then oral methylprednisolone) for a relapse of multiple sclerosis. Fingolimod was discontinued after 317 days of therapy, and intravenous antiviral therapy was started, but the patient died 3 days later. The second death was caused by herpes simplex encephalitis, which developed after 339 days of fingolimod therapy. A 3-day course of intravenous methylprednisolone was initially administered for suspected relapse of multiple sclerosis, followed by antiviral therapy starting 1 week after presentation. The patient died approximately 2 months later.

Two additional patients who received fingolimod at a dose of 1.25 mg died after the study ended. One patient, who had a baseline EDSS score of 5.0 at 3 years after the onset of disease, discontinued fingolimod after 11 months because of neurologic deterioration. Progressive multifocal leukoencephalopathy was ruled out. The patient's condition continued to decline, aspiration pneumonia developed, and the patient died 6 months after study discontinuation. The other patient died from metastatic breast cancer 10 months after discontinuing fingolimod.

### *Infections*

The overall incidence of infection was similar across the study groups (ranging from 51 to 53%), whereas serious infections occurred in 0.2 to 1.7% of patients (Table 3). The only serious infections that were reported in more than one patient were appendicitis and herpesvirus infections. Among patients assigned to receive fingolimod, herpes-


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virus infections were diagnosed in 23 patients in the 1.25-mg group (5.5%) and 9 patients in the 0.5-mg group (2.1%), as well as in 12 patients in the interferon group (2.8%). In 41 of these 44 patients (93%), the infections were mild.

*Cardiovascular Events*

There was a transient, dose-dependent reduction in the heart rate that developed within 1 hour after the initial administration of fingolimod, which is consistent with the findings in previous clinical trials.[12,13,23] Mean maximal decreases were reached after 4 to 5 hours of 12 beats per minute in the group that received the 1.25-mg dose and 8 beats per minute in the group that received the 0.5-mg dose, with the changes starting to attenuate within 6 hours after the first administration of the drug. Most patients had asymptomatic reductions in the heart rate of less than 20 beats per minute. Mild-to-moderate symptomatic bradycardia after the first dose of fingolimod was reported in four patients who received the 1.25-mg dose (0.9%) and in three patients who received the 0.5-mg dose (0.7%). Symptoms resolved within 24 hours without treatment. There were no cases of syncope. Second-degree atrioventricular block was reported during the first day of treatment in four patients receiving fingolimod — three in the 1.25-mg group (0.7%) and one in the 0.5-mg group (0.2%). Two patients in the 1.25-mg group had mild symptoms (intermittent dyspnea and dizziness in one patient and chest pain and palpitations in the other patient), which resolved within 24 hours without treatment. No significant effect on heart rate or atrioventricular conduction was observed with continued administration of the drug. Increases in mean arterial pressure occurred in both fingolimod groups (3 mm Hg in the 1.25-mg group and 2 mm Hg in the 0.5-mg group) during the first 6 months and remained stable between 6 and 12 months.

*Ophthalmologic Events*

Macular edema was confirmed on central review in six patients receiving fingolimod — four in the 1.25-mg group (1%) and two in the 0.5-mg group (0.5%). In three patients, the macular edema was asymptomatic and diagnosed by ophthalmologic examination. Five of the six cases were detected within 4 months after the start of therapy. The edema resolved within 3 months after discontinuation of fingolimod in four patients, was unchanged 1 month after discontinuation in one patient, and was reduced 8 months after discontinuation in one patient. Mean visual acuity and retinal thickness were similar across the study groups and remained stable over the 12-month study period.

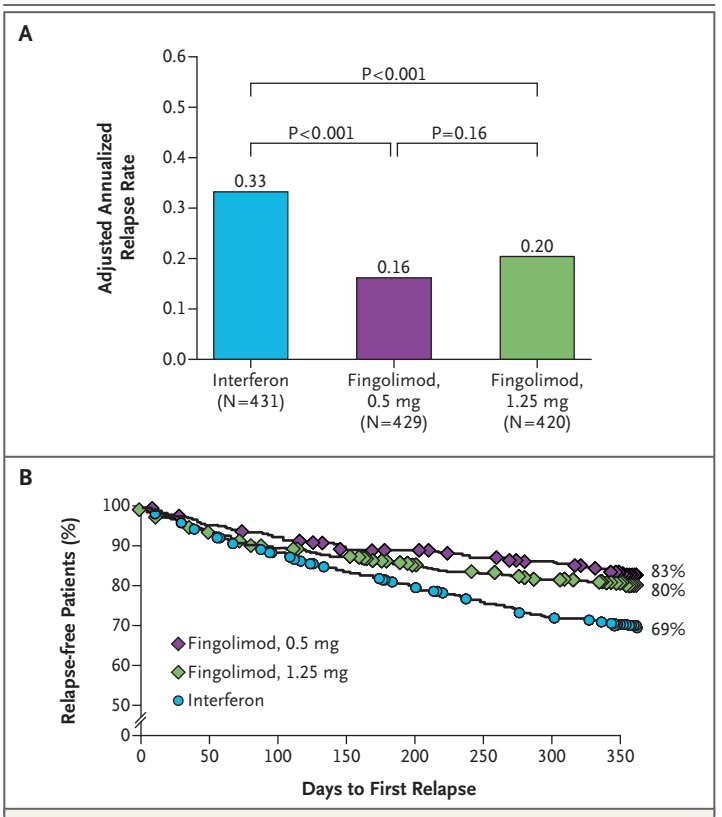


**Figure 2. Annualized Relapse Rate at 12 Months and the Time to the First Relapse.**

Panel A shows the annualized rate of relapse from baseline to 12 months, with adjustment for study group, country, number of relapses in the previous 2 years, and baseline disability score. Panel B shows Kaplan–Meier estimates of the time to the first relapse, indicating the proportion of relapse-free patients (P<0.001 for both comparisons with interferon).

*Neoplasms*

Ten localized skin cancers were reported, and all were successfully excised: five basal-cell carcinomas in the fingolimod groups (two in the 1.25-mg group and three in the 0.5-mg group) and one in the interferon group; three melanomas (all limited to the epidermis) in the group receiving the 0.5-mg dose of fingolimod; and one squamous-cell carcinoma in the interferon group. Of the 10 skin cancers, 8 were diagnosed at the first study examination by a dermatologist 4 to 12 months after enrollment. Breast cancer was reported in two patients in each of the fingolimod groups;

**Table 3. Adverse Events and Serious Adverse Events (Safety Population).***

| Event | Fingolimod | | Interferon Beta-1a (N=431) |
|---|---|---|---|
| | 1.25 mg (N=420) | 0.5 mg (N=429) | |
| | *no. of patients (%)* | | |
| **All adverse events** | | | |
| Any event | 380 (90.5) | 369 (86.0) | 395 (91.6) |
| Any event leading to discontinuation of a study drug | 42 (10.0) | 24 (5.6) | 16 (3.7) |
| **Most frequently reported adverse events** | | | |
| Infection | | | |
| Nasopharyngitis | 93 (22.1) | 88 (20.5) | 88 (20.4) |
| Upper respiratory tract infection | 36 (8.6) | 31 (7.2) | 27 (6.3) |
| Influenza | 28 (6.7) | 29 (6.8) | 32 (7.4) |
| Urinary tract infection | 24 (5.7) | 26 (6.1) | 22 (5.1) |
| Herpesvirus infection | 23 (5.5) | 9 (2.1) | 12 (2.8) |
| Nervous system disorder | | | |
| Headache | 96 (22.9) | 99 (23.1) | 88 (20.4) |
| Dizziness | 23 (5.5) | 24 (5.6) | 21 (4.9) |
| General disorder | | | |
| Fatigue | 59 (14.0) | 44 (10.3) | 45 (10.4) |
| Pyrexia | 15 (3.6) | 18 (4.2) | 77 (17.9) |
| Influenza-like illness | 15 (3.6) | 15 (3.5) | 159 (36.9) |
| Gastrointestinal disorder | | | |
| Diarrhea | 35 (8.3) | 32 (7.5) | 21 (4.9) |
| Nausea | 28 (6.7) | 40 (9.3) | 29 (6.7) |
| Musculoskeletal disorder | | | |
| Back pain | 27 (6.4) | 26 (6.1) | 23 (5.3) |
| Limb pain | 20 (4.8) | 21 (4.9) | 28 (6.5) |
| Arthralgia | 17 (4.0) | 12 (2.8) | 24 (5.6) |
| Myalgia | 14 (3.3) | 14 (3.3) | 44 (10.2) |
| Respiratory disorder | | | |
| Cough | 30 (7.1) | 20 (4.7) | 16 (3.7) |
| Dyspnea | 22 (5.2) | 8 (1.9) | 7 (1.6) |
| Neoplasm | | | |
| Melanocytic nevus | 42 (10.0) | 28 (6.5) | 24 (5.6) |
| Psychiatric disorder | | | |
| Depression | 18 (4.3) | 21 (4.9) | 32 (7.4) |
| Vascular disorder | | | |
| Hypertension | 21 (5.0) | 16 (3.7) | 8 (1.9) |
| Abnormal laboratory value | | | |
| Alanine aminotransferase increased | 24 (5.7) | 28 (6.5) | 8 (1.9) |
| Lymphocytopenia | 4 (1.0) | 1 (0.2) | 0 |



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**Table 3. (Continued.)**

| Event | Fingolimod | | Interferon Beta-1a (N=431) |
|---|---|---|---|
| | 1.25 mg (N=420) | 0.5 mg (N=429) | |
| | *no. of patients (%)* | | |
| **Serious adverse events** | | | |
| Any serious event | 45 (10.7) | 30 (7.0) | 25 (5.8) |
| Death | 2 (0.5)† | 0 | 0 |
| Cardiovascular disorder | | | |
| Bradycardia or sinus bradycardia | 10 (2.4) | 2 (0.5) | 0 |
| Atrioventricular block | | | |
| Second degree | 3 (0.7) | 1 (0.2) | 0 |
| First degree | 2 (0.5) | 1 (0.2) | 0 |
| Infection | | | |
| Appendicitis | 2 (0.5) | 0 | 2 (0.5) |
| Herpesvirus infection | 3 (0.7) | 1 (0.2) | 1 (0.2) |
| Neoplasm | | | |
| Basal-cell carcinoma | 2 (0.5) | 3 (0.7) | 1 (0.2) |
| Melanoma (including in situ) | 0 | 3 (0.7) | 0 |
| Breast cancer (including in situ) | 2 (0.5) | 2 (0.5) | 0 |
| Respiratory disorder | | | |
| Dyspnea | 2 (0.5) | 0 | 0 |

* Listed are all adverse events that occurred in more than 5% of patients in any study group (with the exception of lymphocytopenia), in decreasing order of total frequency. Listed serious adverse events occurred in at least two patients in any study group.

† The two deaths in the group that received fingolimod at a dose of 1.25 mg were caused by disseminated primary varicella zoster infection and herpes simplex encephalitis.

three cases were diagnosed within 4 months after the initiation of the drug, and one was diagnosed 11 months after enrollment.

*Pulmonary Events*

A mild reduction (2 to 3%) in the mean forced expiratory volume in 1 second ($FEV_1$) was observed in both fingolimod groups at 1 month, with no further reductions thereafter. No changes in lung volumes or diffusion capacity were seen.

### LABORATORY MEASUREMENTS

Reflecting fingolimod's mechanism of action, peripheral-blood lymphocyte counts were reduced after 1 month by 77% in the group that received the 1.25-mg dose of fingolimod and by 73% in the group that received the 0.5-mg dose and remained stable thereafter (for details, see the Supplementary Appendix). Alanine aminotransferase levels that were three times the upper limit of the normal range were more frequent in the fingolimod groups (occurring in 29 patients in the 1.25-mg group [7%] and 36 patients in the 0.5-mg group [8%]) than in the interferon group (10 patients [2%]). Alanine aminotransferase levels that were 10 times the upper limit of the normal range occurred in two patients in the interferon group.

## DISCUSSION

This phase 3 study shows the superior efficacy of oral fingolimod over intramuscular interferon beta-1a. Fingolimod reduced the annualized relapse rate to a range of 0.16 to 0.20, as compared with 0.33 for interferon beta-1a, corresponding to a relative reduction of 38 to 52%. No differences were detected in the time to the confirmed progression of disability. The proportion of patients with progression was small in all the study groups, as would be expected in a 12-month study. Fin-

golimod treatment also more effectively reduced lesion activity and brain volume loss on MRI than did interferon beta-1a. The annualized relapse rate for patients receiving intramuscular interferon beta-1a in our study (0.33) was lower than that in several previous studies involving patients with relapsing–remitting multiple sclerosis, in which the rate ranged from 0.61 to 0.77.[22,24-27] This observation suggests that the positive results of our study were not due to enrollment of a population with a large proportion of patients who did not have a response to interferon beta-1a.

The selection of the dose of fingolimod was based on pharmacokinetic and pharmacodynamic considerations from earlier studies,[28] which suggested that a dose of 1.25 mg would be fully effective.[12] The lower dose of 0.5 mg, which was expected to have a submaximal effect on lymphocyte recirculation, was at least as effective, although the 12-month study period may not have been sufficient to show real differences, particularly on disability outcomes.

The adverse events observed in patients receiving fingolimod were consistent with those in previous clinical studies.[12,14,29] Key safety observations included transient bradyarrhythmias, macular edema, infections, and possibly cancers. Effects on the heart rate and atrioventricular conduction appear to be dose-related and result from the modulation of sphingosine-1-phosphate type 1 receptors in cardiac tissue.[30] The mechanism by which macular edema occurs in patients receiving fingolimod requires further study. The onset of such events is early in the course of therapy, and most events improve or resolve after discontinuation of the drug.

Mild and moderate upper and lower respiratory tract infections were slightly more frequent among patients receiving fingolimod. Herpesvirus infections were most common in the 1.25-mg group and were fatal in two patients. The substantial decrease in peripheral-blood lymphocyte counts that is associated with fingolimod therapy reflects redistribution to lymph nodes, rather than destruction of lymphocytes. Thus, patients receiving fingolimod may have preservation of many aspects of immune function, including the total number of lymphocytes, the capacity for lymphocyte activation in lymph nodes and tissues, the capacity for generating antibodies, and innate immune responses.[31] Nevertheless, our findings suggest that fingolimod may be associated with an increased risk of certain viral infections, particularly herpesvirus infections.

After skin cancer was reported in the phase 2 study of fingolimod,[12,29] regular dermatologic monitoring was included in our study. All of the 10 identified skin cancers were successfully excised. Four breast carcinomas were reported in patients in our study who were receiving fingolimod, two in each dose group. One patient died from metastatic disease, and the other three patients had ductal carcinomas diagnosed on routine examinations within 4 months after starting fingolimod. The overall number of cancers was too small to determine causality, and to date there has been no apparent relationship between the dose of fingolimod and the risk of cancer.

Although this is one of the largest studies involving patients with multiple sclerosis to date, a potential shortcoming is that rare or late-appearing adverse events may not have been detected because of their low incidence and the 1-year study duration. Integrated analyses of data from other phase 3 studies and from the extensions of the phase 2 and phase 3 studies will help refine the safety profile of fingolimod, including a possible increase in the risk of cancer.

An oral treatment option for relapsing–remitting multiple sclerosis is highly desirable to improve convenience, diminish side effects, and improve compliance.[32-34] This study showed that once-daily oral fingolimod had superior efficacy to interferon beta-1a administered by weekly intramuscular injection. Fingolimod was associated with clearly identified adverse events, some of which may be dose-related. The absence of dose-related differences in efficacy in this study requires further evaluation in the 2-year, placebo-controlled phase 3 trials.

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## APPENDIX

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