ORIGINAL ARTICLE

Trial of Fingolimod versus Interferon Beta-1a in Pediatric Multiple Sclerosis

Tanuja Chitnis, M.D., Douglas L. Arnold, M.D., Brenda Banwell, M.D., Wolfgang Brück, M.D., Angelo Ghezzi, M.D., Gavin Giovannoni, M.D., Benjamin Greenberg, M.D., Lauren Krupp, M.D., Kevin Rostásy, M.D., Marc Tardieu, M.D., Emmanuelle Waubant, M.D., Jerry S. Wolinsky, M.D., Amit Bar-Or, M.D., Tracy Stites, Ph.D., Yu Chen, M.Sc., Norman Putzki, M.D., Martin Merschhemke, M.D., and Jutta Gärtner, M.D., for the PARADIG*MS* Study Group*

ABSTRACT

BACKGROUND

Treatment of patients younger than 18 years of age with multiple sclerosis has not been adequately examined in randomized trials. We compared fingolimod with interferon beta-1a in this population.

METHODS

In this phase 3 trial, we randomly assigned patients 10 to 17 years of age with relapsing multiple sclerosis in a 1:1 ratio to receive oral fingolimod at a dose of 0.5 mg per day (0.25 mg per day for patients with a body weight of ≤40 kg) or intramuscular interferon beta-1a at a dose of 30 μg per week for up to 2 years. The primary end point was the annualized relapse rate.

RESULTS

Of a total of 215 patients, 107 were assigned to fingolimod and 108 to interferon beta-1a. The mean age of the patients was 15.3 years. Among all patients, there was a mean of 2.4 relapses during the preceding 2 years. The adjusted annualized relapse rate was 0.12 with fingolimod and 0.67 with interferon beta-1a (absolute difference, 0.55 relapses; relative difference, 82%; P<0.001). The key secondary end point of the annualized rate of new or newly enlarged lesions on T_2-weighted magnetic resonance imaging (MRI) was 4.39 with fingolimod and 9.27 with interferon beta-1a (absolute difference, 4.88 lesions; relative difference, 53%; P<0.001). Adverse events, excluding relapses of multiple sclerosis, occurred in 88.8% of patients who received fingolimod and 95.3% of those who received interferon beta-1a. Serious adverse events occurred in 18 patients (16.8%) in the fingolimod group and included infection (in 4 patients) and leukopenia (in 2 patients). Six patients had convulsions. Serious adverse events occurred in 7 patients (6.5%) in the interferon beta-1a group and included infection (in 2 patients) and supraventricular tachycardia (in 1 patient).

CONCLUSIONS

Among pediatric patients with relapsing multiple sclerosis, fingolimod was associated with a lower rate of relapse and less accumulation of lesions on MRI over a 2-year period than interferon beta-1a but was associated with a higher rate of serious adverse events. Longer studies are required to determine the durability and safety of fingolimod in pediatric multiple sclerosis. (Funded by Novartis Pharma; PARADIG*MS* ClinicalTrials.gov number, NCT01892722.)

From the Partners Pediatric Multiple Sclerosis Center, Massachusetts General Hospital, Boston (T.C.); Montreal Neurological Institute, McGill University, and NeuroRx Research — both in Montreal (D.L.A.); Children's Hospital of Philadelphia (B.B.) and the Center for Neuroinflammation and Experimental Neurotherapeutics and the Department of Neurology (A.B.-O.), Perelman School of Medicine, University of Pennsylvania — all in Philadelphia; the Department of Neuropathology (W.B.) and the Department of Pediatrics and Adolescent Medicine, German Center for Multiple Sclerosis in Childhood and Adolescence (J.G.), University Medical Center Göttingen, Göttingen, and the Division of Pediatric Neurology, Children's Hospital Datteln, Witten/Herdecke University, Datteln (K.R.) — all in Germany; Gallarate Hospital, Gallarate, Italy (A.G.); Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London (G.G.); the University of Texas Southwestern Medical Center, Children's Health, Dallas (B.G.), and McGovern Medical School, University of Texas Health Science Center at Houston, Houston (J.S.W.) — both in Texas; Pediatric Multiple Sclerosis Center at NYU Langone, New York (L.K.); Hôpitaux Universitaires Paris-Sud, Assistance Publique–Hôpitaux de Paris, Paris (M.T.); the Department of Neurology, University of California at San Francisco, San Francisco (E.W.); Novartis Pharmaceuticals, East Hanover, NJ (T.S., Y.C., N.P.); and Novartis Pharma, Basel, Switzerland (M.M.). Address reprint requests to Dr. Chitnis at Massachusetts General Hospital, ACC708, 55 Fruit St., Boston, MA 02114, or at tchitnis@rics.bwh.harvard.edu.

*A complete list of the PARADIG*MS* Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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Multiple sclerosis typically appears in young adulthood, but approximately 3% to 5% of cases have an onset that occurs in childhood or adolescence,[1-4] usually with a relapsing–remitting pattern.[5] Relapse rates during the first 6 years of the disease are more than twice as high among pediatric patients as among adult patients, and relapses may be more severe; however, most children and adolescents recover from their initial and subsequent attacks.[6-10] The progression of multiple sclerosis is slower in children than in adults, and both the time to accrue physical disability and the time to reach a secondary progressive phase of the disease are longer for pediatric-onset multiple sclerosis than for adult-onset multiple sclerosis.[11,12] Patients with pediatric-onset multiple sclerosis take approximately 10 years longer than patients with adult-onset multiple sclerosis to reach a phase of secondary progression and of irreversible disability, although they do so at a chronological age approximately 10 years younger than those with adult-onset disease.[12]

Most first-line injectable disease-modifying therapies that are used in adults with multiple sclerosis have been approved by the European Medicines Agency (EMA) for use in children older than 12 years of age.[5,13] Data on the presumed efficacy and safety of these therapies in pediatric patients with multiple sclerosis are derived from retrospective and open-label studies, not from randomized, controlled trials,[14-16] and no disease-modifying therapies have yet been approved by the Food and Drug Administration (FDA) for persons younger than 18 years of age.

Fingolimod is an oral sphingosine-1-phosphate–receptor modulator that is used for relapsing forms of multiple sclerosis. In phase 3 trials involving adult patients with relapsing–remitting multiple sclerosis,[17-19] fingolimod at a dose of 0.5 mg once daily was associated with a significantly lower rate of relapse and significantly lower risk of disability progression than placebo.[17] We undertook a randomized, double-blind, active-controlled, parallel-group trial (PARADIGMS) of fingolimod as compared with intramuscular interferon beta-1a in pediatric patients with multiple sclerosis.

METHODS

TRIAL OVERSIGHT

Novartis Pharma, the sponsor, developed the trial design in collaboration with an advisory group, members of the International Pediatric Multiple Sclerosis Study Group (http://ipmssg.org/), the EMA, and the FDA. Trial drugs were supplied by the sponsor. Data were collected by the investigators and analyzed by the sponsor; the results were reviewed by the sponsor and the advisory group, and safety data were reviewed in an unblinded fashion throughout the trial by a data and safety monitoring board. Confidentiality agreements relating to disclosure of data are in place between the sponsor and the members of the advisory group, all of whom are authors not employed by the sponsor. All the authors, including those employed by the sponsor, had full access to the data and were involved in writing the first draft of the manuscript. Professional medical writing and editorial assistance was paid for by the sponsor. All the authors vouch for the accuracy and completeness of the data and analyses and the reporting of adverse events and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org.

The trial was conducted in accordance with the provisions of the International Conference on Harmonisation guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki.[20] The trial protocol was approved by an institutional review board or ethics committee at each trial site. All the patients or their legal representatives gave written informed consent before any trial-related procedures were performed.

PATIENTS

The trial enrolled patients 10 to 17 years of age with a diagnosis of multiple sclerosis, as defined by the revised consensus definition for pediatric multiple sclerosis,[21] who had had at least one relapse of multiple sclerosis in the year preceding screening or at least two relapses in the 2 years preceding screening, or had evidence of at least one gadolinium-enhancing lesion on T_1-weighted magnetic resonance imaging (MRI) in the 6 months before randomization, and who had an Expanded Disability Status Scale (EDSS) score of 0.0 to 5.5 (range, 0 to 10 in 0.5-unit increments, with higher scores indicating greater disability).[22] Exclusion criteria are listed in the Supplementary Appendix, available at NEJM.org.

TRIAL DESIGN

This was a randomized, multicenter, double-blind, active-controlled, parallel-group trial. Patients underwent assessment during a screening

and baseline period to confirm eligibility, which included central review of the diagnosis of pediatric multiple sclerosis by independent experts, on the basis of the patient's clinical history and MRI scans. Patients were randomly assigned with the use of an interactive voice-response system to receive oral fingolimod (0.5 mg once daily, or 0.25 mg once daily for patients with a body weight of ≤40 kg) or intramuscular interferon beta-1a (30 μg once weekly) for up to 24 months (Fig. S1 in the Supplementary Appendix), with a double-dummy design that used matching placebo capsules and placebo prefilled syringes for intramuscular injection. Randomization was stratified according to geographic region and pubertal status (see the Supplementary Appendix for details of randomization).

The trial regimen was discontinued if the investigator determined that its continuation posed a risk to the patient. Conditions that resulted in permanent discontinuation of the trial regimen included elevated liver aminotransferase levels, macular edema, cardiac arrhythmias or electrocardiographic (ECG) abnormalities, and pregnancy (see the Supplementary Appendix for details of discontinuation criteria).

END POINTS

The primary end point was the annualized relapse rate, defined as the average number of confirmed relapses per year over the period of active treatment. A relapse was confirmed by an independent physician, who was unaware of the trial-group assignments, on the basis of at least a 0.5-point increase in the EDSS score, or a 1-point increase in two functional system (FS) scores, or a 2-point increase in one FS score (excluding the bowel and bladder FS and the cerebral FS), as compared with the most recent evaluation of the EDSS score that did not occur during a relapse.

The key secondary end point was the annualized rate of new or newly enlarged lesions detected on T_2-weighted MRI as compared with baseline. The other secondary end points were the time to the first confirmed relapse, the percentage of patients free of relapse, the number of gadolinium-enhancing lesions, the volume of these lesions, the percentage of patients free of these lesions, and the safety and side-effect profile of the two drugs in all the patients who received treatment for up to 24 months. Safety assessments that were conducted by the investigators or a specialist physician in the relevant medical field included adverse-event monitoring, physical examination (including skin assessment by a dermatologist or pediatrician), assessment for bradycardia at the first dose of the trial regimen, evaluation of vital signs, ECG, routine blood laboratory evaluations, assessment of pulmonary function, assessment of physical and sexual development, ophthalmic examination (by an ophthalmologist), and the Columbia Suicide Severity Rating Scale questionnaire.

Prespecified exploratory end points included the change from baseline in the volume of lesions on T_2-weighted MRI and in the volume of hypointense lesions on T_1-weighted MRI, the number of new hypointense lesions on T_1-weighted MRI, the number of combined unique active lesions (gadolinium-enhancing lesions and newly enlarging lesions on T_2-weighted MRI that were not associated with gadolinium enhancement, or only newly enlarging lesions on T_2-weighted MRI if gadolinium-enhancing lesions were not assessed), and the percentage change in brain volume from baseline. The effect of trial treatments on the time to worsening of disability that persisted for 3 consecutive months from baseline up to month 24 was assessed post hoc.

STATISTICAL ANALYSIS

The sample-size calculation for the primary end point was based on data from the Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing–Remitting Multiple Sclerosis (TRANSFORMS) involving adults with relapsing–remitting multiple sclerosis, which showed a 52% lower annualized relapse rate over a period of 1 year with fingolimod (0.5 mg once daily) than with interferon beta-1a.[18] We estimated that a sample of 95 patients per treatment group would provide the trial with 80% power to detect a 50% relative difference in the annualized relapse rate between the fingolimod group and the interferon beta-1a group over a period of 24 months at a two-sided significance level of 0.05. In a blinded sample-size reestimation, we subsequently determined the 24-month trial to be overpowered owing to a high relapse rate, and the trial design was changed from fixed-duration to flexible-duration in agreement with the EMA and the FDA (see the Supplementary Appendix). At the time point that this protocol amendment was finalized, all the patients had already undergone randomization.

Efficacy end points were analyzed according

to treatment assignment, with the use of two-sided statistical tests when appropriate in the full analysis set, which comprised all randomly assigned patients who took at least one dose of the assigned trial regimen. This differed from the intention-to-treat set by only one patient, who was excluded because of an inability to swallow the first trial-regimen capsule and was withdrawn from the trial without exposure to the trial regimen.

The difference in the annualized relapse rate between the fingolimod group and the interferon beta-1a group was tested with the use of a negative binomial regression model with a log link, including trial regimen, the number of relapses in the 2 years before randomization, pubertal status, and geographic region as covariates. The response variable for this analysis was the number of confirmed relapses for each patient, and the quadratic variance estimate was used. The natural log of time in the trial for each patient was offset for variable treatment duration, under the assumption of noninformative withdrawal from the trial, information missing at random, and a constant relapse rate. Relapses were counted irrespective of whether a patient stopped the trial regimen prematurely. Between-group differences in the key secondary end point (the annualized rate of new or newly enlarged lesions on T_2-weighted MRI from baseline up to 24 months) were tested with the use of negative binomial regression with adjustment for trial regimen, pubertal status, the number of lesions on T_2-weighted MRI at baseline, and geographic region and with the use of the natural log of time (in days) from randomization to the end-of-trial MRI assessment for each patient as the offset variable.

The analyses of the primary and key secondary end points used a prespecified adjustment for multiple comparisons to control the type I error rate, with hypothesis testing conducted at a significance level of 0.05 in the following hierarchical order: treatment effect with respect to the annualized relapse rate, and treatment difference for the annualized rate of new or newly enlarged lesions on T_2-weighted MRI. The lower-ranked test was performed only if the higher-ranked test had a significant result. There was no prespecified plan for adjustment for multiple comparisons for other secondary end points, and results are reported as point estimates with unadjusted confidence intervals only. A post hoc adjustment for multiple comparisons that used the Bonferroni method (to maintain an overall type I error rate of 0.05) was applied to all efficacy end points not included in the prespecified adjustment. The number and percentage of patients with an adverse event were summarized in the safety set (all the patients who received at least one dose of the trial regimen).

RESULTS

PATIENT CHARACTERISTICS

From July 2013 through August 2016, a total of 348 patients were screened (patients could be screened more than once) at 87 centers in 26 countries, and 215 patients were enrolled at 80 centers in 25 countries (7 centers enrolled no patients); 107 patients were randomly assigned to fingolimod and 108 to interferon beta-1a. Of the randomly assigned patients, 188 (87.4%) completed the trial (100 [93.5%] assigned to fingolimod and 88 [81.5%] assigned to interferon beta-1a); 8 patients (7.5%) assigned to fingolimod and 26 patients (24.1%) assigned to interferon beta-1a discontinued the trial regimen prematurely. Of these, 13 patients discontinued interferon beta-1a because of an unsatisfactory therapeutic effect, whereas none discontinued fingolimod for this reason, and 8 patients completed the trial after discontinuing the trial regimen (1 patient [0.9%] in the fingolimod group and 7 patients [6.5%] in the interferon beta-1a group) (Fig. 1).

The mean time from the onset of multiple sclerosis symptoms to entry into the trial was longer in the interferon beta-1a group than in the fingolimod group (2.4 years vs. 1.9 years, P=0.03). There were no significant differences between the two groups in the baseline level of disability (mean EDSS score, 1.5 in the fingolimod group and 1.6 in the interferon beta-1a group) or in the number of relapses before enrollment; 63.3% of patients had not previously received disease-modifying therapies (Table 1, and Table S1 in the Supplementary Appendix). The median duration of exposure to the trial regimen was 634 days in the fingolimod group and 547 days in the interferon beta-1a group (overall median of 587 days or 1.61 years).

EFFICACY

At up to 24 months, the adjusted annualized relapse rate was 0.12 with fingolimod and 0.67

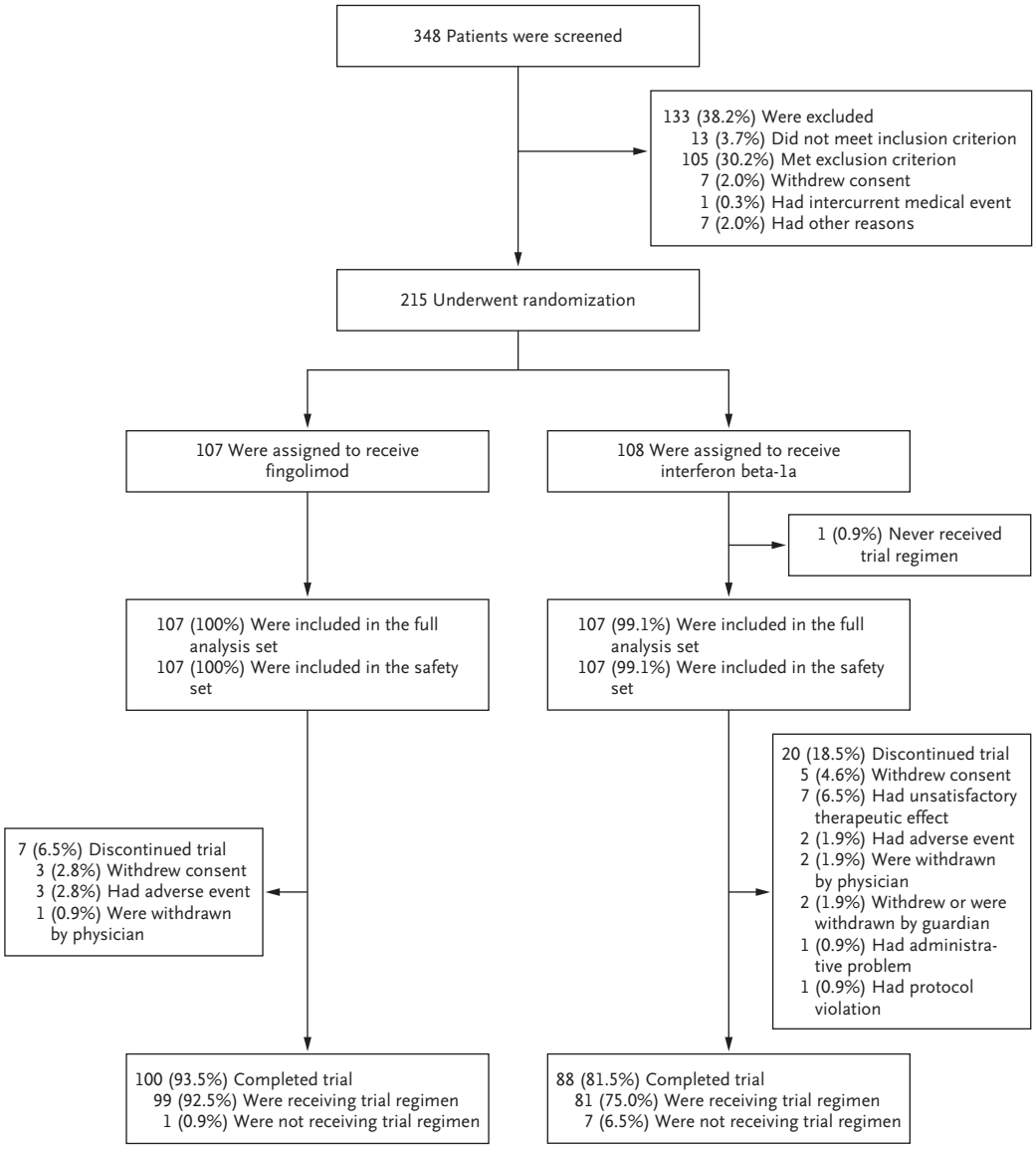


Figure 1. Screening, Randomization, and Follow-up.

Patients who were excluded at screening could be rescreened under a new identification number. The number of screenings represents the number of unique patient identification numbers recorded at screening and rescreening. If rescreening was successful, the identification numbers from both the original screening visit and the rescreening visit were recorded. However, the original identification number was not logged if a patient was excluded at rescreening, so the number of unique patients who were screened cannot be determined. The mean follow-up durations were 612.9 days in the fingolimod group and 557.7 days in the interferon beta-1a group; the median times were 649 days and 561 days, respectively.

with interferon beta-1a (rate ratio, 0.18; 95% confidence interval [CI], 0.11 to 0.30; P<0.001; relative difference, 82%; absolute difference, 0.55 relapses; 95% CI, 0.36 to 0.74; P<0.001) (Table 2). The Kaplan–Meier estimate of the probability of being free of confirmed relapses in each treatment group is shown in Figure 2. The median time to the first confirmed relapse was more than 720 days with fingolimod and was 488 days with interferon beta-1a; the median for fingolimod exceeds the trial duration because the Kaplan–Meier curve did not cross the

Table 1. Baseline Characteristics of the Patients, According to Trial Group (Randomized Set).*

Characteristic	Fingolimod (N=107)	Interferon Beta-1a (N=108)	Total (N=215)
Age — yr			
Mean	15.2±2.0	15.4±1.6	15.3±1.8
Median (range)	16.0 (10–17)	16.0 (11–18)	16.0 (10–18)
Female sex — no. (%)	70 (65.4)	64 (59.3)	134 (62.3)
Pubertal status — no. (%)†			
Prepubertal: Tanner staging score <2	7 (6.5)	3 (2.8)	10 (4.7)
Pubertal: Tanner staging score ≥2	98 (91.6)	105 (97.2)	203 (94.4)
Missing data	2 (1.9)	0	2 (0.9)
Duration of MS since diagnosis — yr			
Mean	1.1±1.3	1.4±1.5	1.2±1.4
Median (range)	0.7 (0.1–8.2)	0.8 (0.1–6.7)	0.7 (0.1–8.2)
Duration of MS since onset of symptoms — yr			
Mean	1.9±1.7	2.4±2.1	2.1±1.9
Median (range)	1.2 (0.2–9.0)‡	1.8 (0.3–10.9)‡	1.5 (0.2–10.9)
Treatment history — no. (%)			
No previous treatment	69 (64.5)	67 (62.0)	136 (63.3)
Any disease-modifying therapy	38 (35.5)	41 (38.0)	79 (36.7)
Any interferon	34 (31.8)	35 (32.4)	69 (32.1)
Any other disease-modifying therapy	8 (7.5)	11 (10.2)	19 (8.8)
No. of relapses in the 2 yr before screening			
Mean	2.4±1.4	2.5±1.3	2.4±1.4
Median (range)	2.0 (0–8)	2.0 (1–9)	2.0 (0–9)
No. of gadolinium-enhancing lesions			
Patients evaluated	106§	107§	213
Mean	2.6±6.0	3.1±6.5	2.9±6.2
Median (range)	1.0 (0–52)	0.0 (0–37)	1.0 (0–52)
Patients free of gadolinium-enhancing lesions — no./total no. (%)	47/106 (44.3)	59/107 (55.1)	106/213 (49.8)
Volume of lesions on T_2-weighted MRI			
Patients evaluated	107	107§	214
Mean — mm^3	8902±13,148	11,512±15,087	10,207±14,178
Median (range) — mm^3	5245 (52–116,533)	6197 (189–101,099)	5548 (52–116,533)
Whole-brain volume			
Patients evaluated	107	105§	212
Mean — cm^3	1154±127	1160±122	1157±124
Median (range) — cm^3	1146 (917–1633)	1136 (910–1487)	1139 (910–1633)

* Plus–minus values are means ±SD. Fingolimod was administered orally, and interferon beta-1a was administered intramuscularly. MRI denotes magnetic resonance imaging, and MS multiple sclerosis.

† Tanner staging scores (range, 1 to 5, with 1 indicating prepubertal and 5 fully pubertal) were based on the higher of two scores (for breast development and pubic-hair assessment in female patients and for genital stage and for pubic-hair assessment in male patients). A bone age of at least 16 years or menarche for female patients was considered to be pubertal if the Tanner staging score was missing.

‡ P=0.03 for the comparison between groups.

§ Baseline information was missing for a small number of patients because no assessment was made before the first dose.

Table 2. Primary and Secondary End Points at Month 24 (Full Analysis Set).

End Point	Fingolimod	Interferon Beta-1a	Rate Ratio (95% CI)	Between-Group Difference (95% CI)
Primary end point				
Patients evaluated	107	107		
Annualized relapse rate (95% CI)*	0.12 (0.08–0.19)	0.67 (0.52–0.89)	0.18 (0.11–0.30)†	0.55 (0.36–0.74)†‡
Key secondary end point				
Patients evaluated	106	102		
Annualized rate of new or newly enlarged lesions on T_2-weighted MRI (95% CI)*	4.39 (3.62–5.37)	9.27 (7.66–11.21)	0.47 (0.36–0.62)†	4.88 (2.91–6.84)†‡
Secondary clinical end point				
Patients evaluated	107	107		
Patients free of relapse — % (95% CI)§	85.7 (79.0–92.4)	38.8 (27.4–50.3)		46.9 (33.7–60.1)
Secondary MRI-related end point				
Patients evaluated	106	101		
Adjusted mean no. of gadolinium-enhancing lesions per scan (95% CI)*	0.44 (0.31–0.61)	1.28 (0.93–1.76)	0.34 (0.22–0.54)	

* Values were determined with the use of a negative binomial regression model (prespecified adjustments for multiple comparisons are described in the Supplementary Appendix).
† P<0.001.
‡ Post hoc analysis of the absolute between-group difference in the annualized relapse rate and in the annualized rate of new or newly enlarged lesions on T_2-weighted MRI was based on normal approximation.
§ Values were estimated at month 24 by means of Kaplan–Meier analysis.

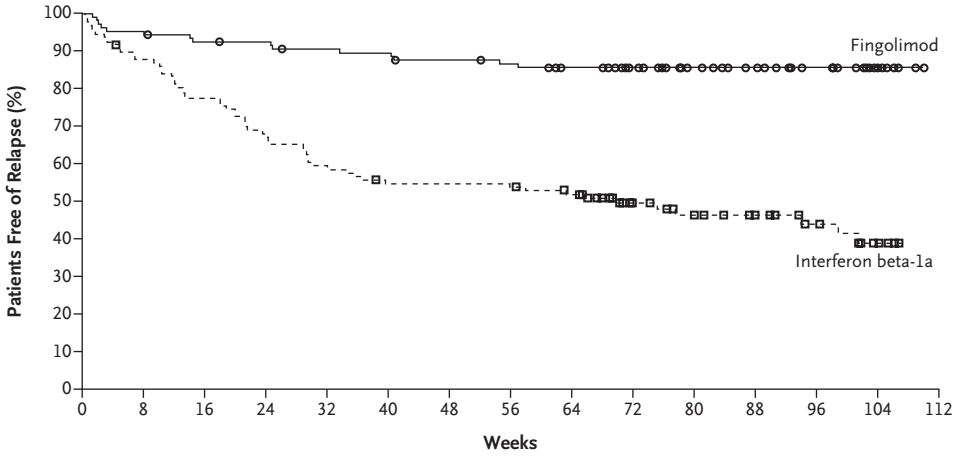
50% threshold (hazard ratio, 0.18; 95% CI, 0.10 to 0.32; P<0.001). The Kaplan–Meier estimate of the percentage of patients free of relapse at month 24 (a secondary end point) was 85.7% in the fingolimod group and 38.8% in the interferon beta-1a group (difference, 46.9 percentage points; unadjusted 95% CI, 33.7 to 60.1).

The key secondary end point of the annualized rate of new or newly enlarged lesions on T_2-weighted MRI at up to 24 months was 4.39 with fingolimod and 9.27 with interferon beta-1a (rate ratio, 0.47; 95% CI, 0.36 to 0.62; P<0.001; relative difference, 53%; absolute difference, 4.88 lesions; 95% CI, 2.91 to 6.84; P<0.001). The mean number of gadolinium-enhancing lesions per scan at up to 24 months was 0.44 with fingolimod and 1.28 with interferon beta-1a (rate ratio, 0.34; unadjusted 95% CI, 0.22 to 0.54) (Table 2). In prespecified exploratory analyses, the rate of brain-volume change was −0.48% with fingolimod and −0.80% with interferon beta-1a (least-squares mean difference for fingolimod vs. interferon beta-1a, 0.32 percentage points; 95% CI, 0.06 to 0.57) (Table S2 in the Supplementary Appendix).

In post hoc analyses, fingolimod delayed the time to a worsening of disability that was confirmed at 3 months as compared with interferon beta-1a (Fig. S2 in the Supplementary Appendix). Secondary clinical and MRI-related end points were significantly different between the treatment groups when post hoc adjustment for multiple comparisons was performed with the use of Bonferroni's method (adjusted P=0.003); P values for these end points are not reported because there was no prespecified adjustment for multiple comparisons for these outcomes.

SAFETY

The overall incidence of adverse events was 88.8% in the fingolimod group and 95.3% in the interferon beta-1a group; adverse events reported in at least 10% of patients receiving fingolimod or interferon beta-1a are shown in Table 3, and adverse events that occurred in at least two patients in any treatment group and were reported more frequently with fingolimod than with interferon beta-1a are shown in Table S3 in the Supplementary Appendix. To account for the unbalanced exposure to the trial regimen resulting from premature discontinuations in the interferon beta-1a group, exposure-adjusted incidence



No. at Risk

Fingolimod	107	102	98	97	94	93	90	88	84	72	59	53	45	15	0
Interferon beta-1a	107	93	82	71	63	57	57	56	52	35	27	23	18	8	0

Figure 2. Time to the First Confirmed Relapse and Percentage of Patients Free of Relapse.

The time to the first confirmed relapse was significantly longer in the fingolimod group than in the interferon beta-1a group (P<0.001). The Kaplan–Meier estimate of the percentage of patients free of relapse at month 12 and month 24 was higher in the fingolimod group (87.7% and 85.7%, respectively) than in the interferon beta-1a group (54.7% and 38.8%, respectively), with an 82% risk difference up to month 24 as calculated with a Cox proportional-hazards model (rate ratio, 0.18; P<0.001). Censored data are indicated by circles (in the fingolimod group) and squares (in the interferon beta-1a group).

rates are provided in Table S3 in the Supplementary Appendix. In total, five patients (4.7%) in the fingolimod group and three patients (2.8%) in the interferon beta-1a group had an adverse event leading to discontinuation of the trial regimen.

A total of 18 patients (16.8%) in the fingolimod group and 7 (6.5%) in the interferon beta-1a group had at least one serious adverse event. Convulsions (determined on the basis of a standardized *Medical Dictionary for Regulatory Activities* query) occurred in 6 patients (5.6%) receiving fingolimod and 1 patient (0.9%) receiving interferon beta-1a. Among the 6 patients in the fingolimod group with convulsions, coding of serious adverse events was applied to seizures in 2 patients, generalized tonic–clonic seizure in 1 patient, and epilepsy in 1 patient. Other serious adverse events in the fingolimod group included single cases (0.9%) of agranulocytosis, arthralgia, autoimmune uveitis, bladder spasm, dyspepsia, dysuria, elevated alanine aminotransferase level, elevated γ-glutamyltransferase level, gastrointestinal necrosis (intussusception or necrotic bowel), head injury, humerus fracture, hypersensitivity vasculitis, migraine, migraine without aura, multiple sclerosis plaque, muscular weakness, rectal tenesmus, second-degree atrioventricular block, and small-intestinal obstruction and two cases of leukopenia (1.9%). Overall, 4 patients (3.7%) in the fingolimod group had infections (appendicitis, cellulitis, gastrointestinal infection, oral abscess, viral infection, and viral pharyngitis), as did 2 patients (1.9%) in the interferon beta-1a group (paronychia and viral gastritis). Serious adverse events with interferon beta-1a were single cases (0.9%) of dizziness, fatigue, gastroesophageal reflux disease, headache, increased body temperature, optic neuritis, pyrexia, sensory loss, supraventricular tachycardia, and uveitis. (A single case of seizure with interferon beta-1a was classified as an adverse event and not a serious adverse event.) One patient receiving fingolimod and 3 patients receiving interferon beta-1a had relapses of multiple sclerosis that were unusually severe and hence were reported as serious adverse events in accordance with the trial protocol. Rates of adverse events calculated without these severe relapses are shown in Table 3.

One case of macular edema was reported

Table 3. Adverse Events (Safety Set).*

Event	Fingolimod (N=107)	Interferon Beta-1a (N=107)
	no. of patients (%)	
All events†		
Any adverse event	95 (88.8)	102 (95.3)
Adverse event leading to interruption of trial regimen	12 (11.2)	3 (2.8)
Adverse event leading to discontinuation of trial regimen	5 (4.7)	3 (2.8)
Any serious adverse event	18 (16.8)	7 (6.5)
Adverse events reported in ≥10% of patients in either group and adverse events of special interest		
Alanine aminotransferase increased	4 (3.7)	5 (4.7)
Aspartate aminotransferase increased	0	5 (4.7)
Chills	1 (0.9)	11 (10.3)
Cough	10 (9.3)	12 (11.2)
γ-Glutamyltransferase increased	4 (3.7)	0
Headache	34 (31.8)	32 (29.9)
Influenza	12 (11.2)	4 (3.7)
Influenza-like illness	5 (4.7)	40 (37.4)
Leukopenia	15 (14.0)	3 (2.8)
Pyrexia	8 (7.5)	22 (20.6)
Upper respiratory tract infection	17 (15.9)	5 (4.7)
Viral upper respiratory tract infection	23 (21.5)	26 (24.3)
White-cell count decreased	6 (5.6)	0

* Adverse events were coded according to the preferred terms in the *Medical Dictionary for Regulatory Activities*, version 20.0.
† Excluded were relapses of multiple sclerosis that were reported as adverse events.

with fingolimod, and a single case of uveitis was reported in each group. One case of Mobitz type I second-degree atrioventricular block occurred during dose adjustment of fingolimod, and one case of supraventricular tachycardia occurred with interferon beta-1a. Elevated levels of alanine aminotransferase and γ-glutamyltransferase (up to 11.9 times the upper limit of the normal range) occurred in one patient receiving fingolimod. The case of agranulocytosis occurred in a patient who had been using fingolimod for 6 months and after she had received a 3-week course of lymecycline for acne. The patient later had treatment with fingolimod reinitiated and completed the trial while receiving the drug without recurrent agranulocytosis. No opportunistic infections or cancers were reported in either group, and there were no deaths during the trial period.

DISCUSSION

This double-blind, active-comparator trial showed superior efficacy of fingolimod over interferon beta-1a in reducing relapses in children and adolescents with multiple sclerosis who received treatment for a median of 1.61 years. Relapse rates with fingolimod in our trial were similar to those seen among adults in phase 3 trials of fingolimod.[17-19] In contrast, the annualized relapse rate in the interferon beta-1a group was approximately twice that seen among adult patients who received interferon beta-1a in TRANSFORMS[18] and was more than 1.5 times that seen among adults who received placebo in the FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis (FREEDOMS) trials.[17,19] Relapse rates approximately 2 to 3 times as high as those seen among adult patients have

been reported in trials of pediatric-onset multiple sclerosis.[7,10] In our trial, relapse frequencies were similar in the two treatment groups before randomization, and at randomization, the percentage of patients who were free of gadolinium-enhancing lesions was higher in the interferon beta-1a group than in the fingolimod group. Therefore, the between-group difference in relapses at up to 24 months is not likely to reflect an imbalance in the trajectory of multiple sclerosis between the two groups at baseline.

Given the high rate of relapse among pediatric patients, interferon may be considered to be a weak comparator against which to assess the efficacy of fingolimod. However, interferon is used as a standard of care for pediatric multiple sclerosis[13,14,23] and has regulatory approval for use by the EMA in adolescents older than 12 years of age. A smaller difference in the treatment effect between fingolimod and interferon beta-1a was observed in TRANSFORMS, which had a design similar to that of our trial but which involved adult, rather than pediatric, patients.[18] Published data suggest that the magnitude of the treatment effect, in terms of the percentage reduction in the annualized relapse rate, may be inversely proportional to patient age.[24]

The incidence of serious adverse events was higher with fingolimod than with interferon beta-1a. In the fingolimod group, leukopenia was presumably related to lymphocyte sequestration, which is attributable to the mode of action of fingolimod. A reduction in peripheral lymphocyte counts may increase the risk of infection,[25] and infections that were reported as serious adverse events were more frequent with fingolimod than with interferon beta-1a. Influenza-like illness was the most common adverse event associated with interferon beta-1a in this trial, a finding consistent with those of other trials.[26] Six patients receiving fingolimod and one patient receiving interferon beta-1a had a seizure during the trial. Seizures may be a more important side effect in pediatric patients receiving fingolimod than in adults and may need to be monitored in subsequent trials. There were no reports of skin carcinomas, an increased risk of which has been associated with fingolimod among adults, but longer monitoring may be necessary to assess dermatologic risks.[25]

Fewer patients prematurely discontinued fingolimod than interferon beta-1a; about half of those discontinuing interferon beta-1a did so because their physicians, who were unaware of the trial-group assignments, judged the therapeutic effect to be unsatisfactory. Longer-duration trials are needed to determine the durability and the safety of fingolimod in the pediatric population with multiple sclerosis. An open-label 5-year extension trial involving the population in the current trial is ongoing (ClinicalTrials.gov number, NCT01892722).

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