Supplemental data

e-Methods (not reported in main manuscript)

Randomization and masking

The study drug for an individual patient was identified by a label using the assigned randomization number. Immediately before dispensing the study drug to the patient, study staff detached the outer part of the label from the packaging and fixed it to the source document containing that patient's unique patient number. Unblinding during the dose-blinded period of the extension was permitted in the case of patient emergencies only. Following a recommendation from the independent data and safety monitoring board, the fingolimod 1.25 mg/day dose was discontinued from all multiple sclerosis (MS) clinical studies. The conversion of individuals randomized to the fingolimod 1.25 mg dose group to the fingolimod 0.5 mg dose followed a protocol amendment dated 4 November 2009. Randomization numbers for the fingolimod 1.25 mg dose group were provided by Novartis to the study sites then individual participants were identified and invited to the study site for an unscheduled visit in order to be converted to fingolimod 0.5 mg/day. At this visit, patients also returned any unused study medication provided previously.

Drug administration

Fingolimod was to be taken orally once a day, preferably at the same time each day. The first dose of study drug during the extension phase was to be taken in the clinic on

the day after the last dose of study drug was taken in the 24-month FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis) trial. If dose interruption between FREEDOMS and its extension could not be avoided, it should not have exceeded 14 days. Dose adjustments were not allowed; however, drug interruptions were allowed based on the judgment of the investigator.

Procedures and assessments

In the event of premature withdrawal from the study, the end of extension study (EoS) visit was to be completed. If the patient was unable to return for the EoS visit, every effort should have been made to contact the individual by telephone for safety evaluations during the 30 days following the last dose of study drug. For the extension phase, patients who discontinued study drug were considered withdrawn from the study. Individuals who did not continue treatment with fingolimod were scheduled for a follow-up visit 3 months after the last dose of extension study drug to assess safety (including lymphocyte counts) and efficacy parameters after fingolimod treatment discontinuation. There was no follow-up visit for participants who continued treatment with commercial fingolimod or those who transferred into the long-term umbrella extension study (ClinicalTrials.gov number NCT01201356).[1]

In addition to the evaluations outlined in the main manuscript, a complete physical assessment was performed every 6 months starting at month 30, with a final examination at EoS. The examination included an assessment of skin, head and neck, lymph nodes, breast, heart, lungs, abdomen, and back, and comments on general appearance. Participants were recommended to continue to perform skin self-

examination on a monthly basis, as performed during FREEDOMS. At each regular visit throughout the extension phase, the primary treating physician asked the patient about any new skin lesion or changes in previously existing skin lesions that the individual had identified by skin self-examination (referral to a dermatologist was made when appropriate). In addition, examination by a dermatologist was performed at month 36 and then every 12 months and at EoS. Ophthalmic examinations and pulmonary function tests were performed at months 25, 27, and 30, and then every 6 months until EoS. Ophthalmic examination included eye history, visual acuity, and dilated ophthalmoscopy. All patients were required to undergo optical coherence tomography assessment to evaluate macular thickness at EoS.

First-dose monitoring

Sitting heart rate and blood pressure were assessed before the first dose and every hour for at least 6 hours after the first dose. Electrocardiograms (ECGs) were also recorded pre- and post-dose. Patients were discharged after administration of the first dose when all of the following criteria were met: heart rate of at least 51 beats per minute, heart rate more than 80% of baseline value, heart rate at discharge not the lowest hourly value of the monitoring period, no symptoms of decreased heart rate, no treatment for bradycardia received, and ECG at 6 hours did not show any significant abnormalities vs pre-dose other than sinus bradycardia. Patients experiencing symptomatic reductions in heart rate were hospitalized overnight.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) was carried out according to a standard protocol. T1-weighted images, before and after administration of single-dose gadolinium (Gd) diethylenetriamine penta-acetic acid (0.1 mmol/kg), and dual-echo T2-weighted images were obtained. Numbers of new or enlarged T2 lesions, number and volume of Gd-enhancing T1 lesions, total volume of T2 lesions, total volume of T1 hypointense lesions, and brain volume at baseline and change over time were obtained according to a standard protocol, as previously described.[2] Each MRI scan performed for the patient was reviewed by a local neuroradiologist; the primary treating physician was contacted in any case in which unexpected findings were detected. The scans were processed centrally at the MS MRI Evaluation Center (Basel, Switzerland). The central reader checked the scans for completeness and quality. To avoid interference caused by corticosteroids for the treatment of MS relapses, scheduling of MRI scans could be adjusted so as to be performed before initiation of steroid treatment or not until 30 days after its termination.

Statistical analyses

Covariates included in binomial regression analyses were selected based on their clinical relevance and on findings from previous (phase 1 and phase 2) clinical studies. Annualized relapse rates (ARRs) were compared between groups using a negative binomial regression model adjusting for treatment, country, number of relapses in the 2 years before enrollment, and FREEDOMS baseline Expanded Disability Status Scale

(EDSS) score. Within-group comparisons of ARRs were performed using the Wilcoxon signed-rank test. The times to first confirmed MS relapse, and first 3-month (or 6-month) confirmed disability progression to EoS were analyzed using the Kaplan–Meier method, and the log-rank test was used to compare the survival distributions between groups. The Kaplan–Meier estimates of the proportion of patients who were relapse-free, or free of disability progression, and the 95% confidence intervals (CIs) were also calculated for each treatment group. Additionally, the time to first confirmed MS relapse was analyzed using the Cox proportional hazard model adjusted for treatment, country, number of relapses in the 2 years before enrollment, and FREEDOMS baseline EDSS score. The time to first 3-month (or 6-month) confirmed disability progression was analyzed using the Cox proportional hazard model adjusted for treatment, country, FREEDOMS baseline EDSS score and age. The hazard ratios and their 95% CIs were calculated.

The numbers of new or newly enlarged T2 lesions were compared between groups using a negative binomial regression adjusted for treatment, country, and T2 lesion volume at FREEDOMS baseline; within-group comparisons of number of new or newly enlarged T2 lesions were performed using the Wilcoxon signed-rank test. Within-group comparisons of the number of patients free from new or newly enlarged T2 lesions were performed using McNemar's test. Between-group comparisons of the number of Gd-enhancing T1 lesions were compared using rank analysis of covariance (rank ANCOVA), adjusting for treatment, country, and number of Gd-enhancing T1 lesions at FREEDOMS baseline; within-group comparisons of number of Gd-enhancing T1 lesions were performed using the Wilcoxon signed-rank test. Within-group comparisons of the

number of patients free from Gd-enhancing T1 lesions were performed using McNemar's test. Between-group comparisons of percentage change in normalized brain volume were performed using rank ANCOVA, adjusting for treatment, country, and brain volume normalized at FREEDOMS baseline; within-group comparisons were performed using the Wilcoxon signed-rank test.

e-Results (not reported in the main manuscript)

Disability outcomes

Mean changes from FREEDOMS baseline to EoS in EDSS score (0.06 [SD 1.05] for continuous fingolimod 0.5 mg; 0.06 [1.07] for continuous fingolimod 1.25 mg; 0.15 [1.07] for the combined placebo–fingolimod switch group) and Multiple Sclerosis Functional Composite (MSFC) *z*-score (−0.007 [0.976] for continuous fingolimod 0.5 mg; −0.110 [0.831] for continuous fingolimod 1.25 mg; −0.088 [0.609] for the combined placebo–fingolimod switch group) did not differ significantly between continuous and switch groups. In the switch groups, EDSS and MSFC scores did not differ significantly between FREEDOMS and its extension; changes in EDSS and MSFC scores during the extension were minimal.

Laboratory evaluations

In the switch groups, alanine aminotransferase, aspartate aminotransferase, and γ-glutamyltransferase levels increased during the extension, reaching maximum levels approximately 3 months after the first fingolimod dose and remaining stable thereafter. In the continuous treatment groups, levels of these enzymes remained stable during the

extension and did not increase over time. By 2 weeks after the first fingolimod dose, mean absolute lymphocyte counts were reduced in both switch groups: to 0.602×10^9/L (33.2% of FREEDOMS baseline) in the fingolimod 0.5 mg group, and 0.471×10^9/L (25.7% of FREEDOMS baseline) in the fingolimod 1.25 mg group). By contrast, counts in the continuous treatment groups remained at the same level (slightly reduced from FREEDOMS baseline) throughout the extension phase.

Efficacy and safety among enrollers and non-enrollers

Among the eligible patients who chose not to enrol in the extension (n=113), proportionately more had received fingolimod 1.25 mg during FREEDOMS (n [%], 43 [13.0]) than had received fingolimod 0.5 mg (n [%], 38 [10.3]) or placebo (n [%], 32 [9.6]). Both enrollers and non-enrollers on fingolimod experienced a significant treatment benefit at the end of FREEDOMS, in terms of lower ARR compared with those on placebo: enrollers (ARR ratio [95%CI]): fingolimod 0.5 mg, 0.516 (0.402, 0.662); 1.25 mg, 0.303 (0.224, 0.4090; p<0.001, both); non-enrollers: fingolimod 0.5 mg, 0.256 (0.122, 0.538; p<0.001); 1.25 mg, 0.451 (0.248, 0.820; p=0.009).

Generally, there were proportionately fewer non-enrollers than enrollers who were free from confirmed disability progression, and the non-enrollers were generally less likely to have seen a treatment benefit with fingolimod compared with placebo. Respectively among the enrollers and non-enrollers at the end of FREEDOMS, the proportions of patients (95% CI), who were free from disability progression confirmed at 6 months, were: fingolimod 1.25 mg: 91.3% (88.1%, 94.6%) and 83.7% (72.7%, 94.8%); fingolimod 0.5 mg: 89.4% (86.1%, 92.7%) and 81.6% (69.3%, 93.9%); placebo: 83.7%

(79.5%, 87.9%) and 75.0% (60.0%, 90.0%). Compared with placebo, enrollers on fingolimod were more likely to be free from disability progression (fingolimod 1.25 mg, p=0.009; fingolimod 0.5 mg, p = 0.044), but the proportions of non-enrollers free from disability progression were similar in the fingolimod and placebo groups (fingolimod 1.25 mg, p=0.516; fingolimod 0.5 mg, p = 0.150).

In total, there were slightly higher rates of AEs among the non-enrollers than among the enrollers (respectively for all AEs, n [%]): fingolimod 1.25 mg, 42 (97.7%) vs 271 (93.8%); fingolimod 0.5 mg, 37 (97.4%) vs 312 (94.3%); placebo, 32 (100.0%) vs 281 (93.7%). By treatment group, some AEs occurred more frequently among the non-enrollers than the enrollers. Of these, the ones that occurred in at least four non-enrollers in a fingolimod group (approximately 10% of a treatment group) and at a higher rate than in the non-enrollers' placebo group, were: fingolimod 1.25 mg: fatigue; upper respiratory tract infection; weight decrease; headache; cough; and eczema; fingolimod 0.5 mg: diarrhoea; bronchitis; gastroenteritis; increased blood triglycerides; and depression; fingolimod 1.25 mg and 0.5 mg: increased alanine aminotransferase; back pain; and dizziness. The overall rates of these AEs among non-enrollers were broadly similar to those among enrollers.Proportionately more non-enrollers than enrollers experienced SAEs (n [%]): fingolimod 1.25 mg, 10 (23.3%) vs 20 (6.9%); fingolimod 0.5 mg, 6 (15.8%) vs 31 (9.4%); placebo, 6 (18.8%) vs 32 (10.7%), respectively. Among non-enrollers, basal cell carcinoma (n = 4) and MS relapse (n = 2) were reported in both fingolimod groups; all other SAEs were reported once in total.

e-References

1. ClinicalTrials.gov. Long-term safety and tolerability of 0.5 mg fingolimod in patients with relapsing forms of multiple sclerosis. Available at: http://clinicaltrials.gov/show/NCT01201356 Accessed November 21, 2014.
2. Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010;362:387–401.