Comparison of fingolimod with interferon beta-1a in relapsing-remitting multiple sclerosis: a randomised extension of the TRANSFORMS study

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Summary

Background In a 12-month phase 3 study in patients with relapsing-remitting multiple sclerosis (RRMS), TRANSFORMS, fingolimod showed greater efficacy on relapse rates and MRI outcomes compared with interferon beta-1a. We had two aims in our extension: to compare year 2 with year 1 in the switched patients to assess the effect of a change from interferon beta-1a to fingolimod, and to compare over 24 months the treatment groups as originally randomised to assess the effect of delaying the start of treatment with fingolimod.

Methods Patients randomly assigned to receive 0·5 mg or 1·25 mg daily oral fingolimod in the core study continued with the same treatment in our extension; patients who originally received 30 µg weekly intramuscular interferon beta-1a were randomly reassigned (1:1) to receive either 0·5 mg or 1·25 mg fingolimod. The initial randomisation and dose of fingolimod assigned for the extension remained masked to the patients and investigators. As in the core study, re-randomisation was done centrally in blocks of six and stratified according to site. Our efficacy endpoints were annualised relapse rate (ARR), disability progression, and MRI outcomes. Our within-group analyses were based on the intention-to-treat and safety populations that entered our extension study. Our between-group analyses were based on the intention-to-treat and safety populations from the core study. This study is registered with ClinicalTrials.gov, number NCT00340834.

Findings 1027 patients entered our extension and received the study drug, and 882 completed 24 months of treatment. Patients receiving continuous fingolimod showed persistent benefits in ARR (0·5 mg fingolimod [n=356], 0·12 [95% CI 0·08–0·17] in months 0–12 *vs* 0·11 [0·08–0·16] in months 13–24; 1·25 mg fingolimod [n=330], 0·15 [0·10–0·21] *vs* 0·11 [0·08–0·16]; however, in patients who initially received interferon beta-1a, ARR was lower after switching to fingolimod compared with the previous 12 months (interferon beta-1a to 0·5 mg fingolimod [n=167], 0·31 [95% CI 0·22–0·43] in months 0–12 *vs* 0·22 [0·15–0·31], in months 13–24 p=0·049; interferon beta-1a to 1·25 mg fingolimod [n=174], 0·29 [0·20–0·40] *vs* 0·18 [0·12–0·27], p=0·024). After switching to fingolimod, numbers of new or newly enlarging T2 and gadolinium (Gd)-enhancing T1 lesions were significantly reduced compared with the previous 12 months of interferon beta-1a therapy (p<0·0001 for T2 lesions at both doses; p=0·002 for T1 at 0·5 mg; p=0·011 for T1 at 1·25 mg), and the pattern of adverse events shifted towards that typical for fingolimod. Over 24 months, in continuous fingolimod groups compared with the group that switched from interferon beta-1a to fingolimod, we recorded lower ARRs (0·18 [95% CI 0·14–0·22] for 0·5 mg; 0·20 [0·16–0·25] for 1·25 mg; 0·33 [0·27–0·39] for the switch group; p<0·0001 for both comparisons), fewer new or newly enlarged T2 lesions (p=0·035 for 0·5 mg, p=0·068 for 1·25 mg), and fewer patients with Gd-enhancing T1 lesions (p=0·001 for 0·5 mg fingolimod *vs* switch group; p=0·002 for 1·25 mg fingolimod *vs* switch group). There was no benefit on disability progression.

Interpretation Switching from interferon beta-1a to fingolimod led to enhanced efficacy with no unexpected safety concerns. Compared with patients switched from interferon beta-1a to fingolimod, continuous treatment with fingolimod for 2 years provides a sustained treatment effect with improved clinical and MRI outcomes.

Funding Novartis Pharma AG.

Introduction

Fingolimod is the first in a new class of drugs—the sphingosine 1-phosphate receptor modulators—and is approved for the treatment of relapsing multiple sclerosis at a recommended dose of 0·5 mg once daily. The efficacy of fingolimod in relapsing-remitting multiple sclerosis (RRMS) has been shown in a clinical programme that includes two large multicentre phase 3 studies: a 1-year active-controlled study, TRANSFORMS (trial assessing injectable interferon versus FTY720 oral in RRMS),[1] in which fingolimod had better efficacy than a first-line treatment (intramuscular interferon beta-1a) on relapse and MRI outcomes, and a 2-year placebo-controlled study, FREEDOMS (FTY720 research evaluating effects of daily oral therapy in multiple sclerosis),[2] that showed efficacy on relapses, disability

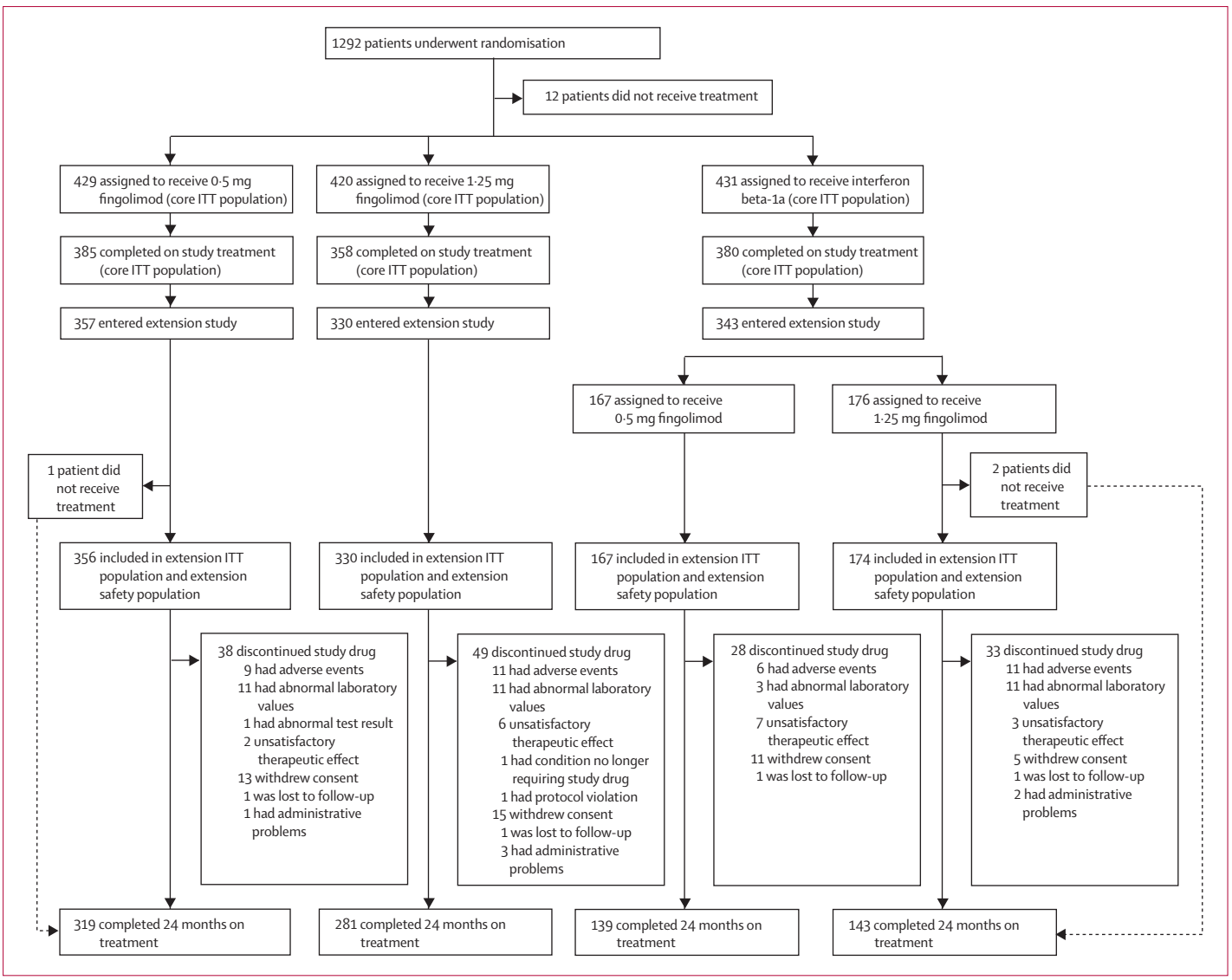

Figure 1: **Trial profile**

Reasons for discontinuation from the core study are available in the TRANSFORMS report by Cohen and colleagues.[1] Only patients who completed the core study on treatment were allowed to enter the extension phase. 28 (0·5 mg fingolimod), 28 (1·25 mg fingolimod), and 37 (interferon beta-1a) patients decided not to enter our extension phase. In our extension, three patients in the continuous fingolimod groups (one on 0·5 mg and two on 1·25 mg) and two in the interferon beta-1a to 1·25 mg fingolimod group were randomised in error and never received treatment. ITT=intention to treat.

progression, and MRI measures. We present results from the second year of TRANSFORMS, a 1-year extension in which patients originally randomly assigned to receive fingolimod continued with treatment at the same dose as in the core study, and patients originally assigned to receive interferon beta-1a in the core study were randomly reassigned to receive fingolimod 0·5 mg or 1·25 mg. We did within-group comparisons to assess the efficacy and safety of fingolimod during months 13–24 compared with months 0–12 in patients who had switched from interferon beta-1a at month 12. We compared groups of patients receiving fingolimod for up to 2 years with patients who switched treatment to assess the effect of delayed onset of fingolimod.

Methods

Participants

Patients eligible for inclusion in the core study: were aged 18–55 years; had a diagnosis of multiple sclerosis in accordance with the 2005 revised McDonald criteria,[3] with a relapsing-remitting disease course; had one or more documented relapses in the year before randomisation or two or more documented relapses in the 2 years before randomisation; had an expanded disability status scale (EDSS) score of 0–5·5;[4] and were neurologically stable, with no evidence of relapse or corticosteroid treatment within 30 days before randomisation.

Key exclusion criteria were: other chronic immune diseases; malignancy; macular oedema; active infection;

	Interferon beta-1a to 0·5 mg fingolimod switch group (n=167)	Interferon beta-1a to 1·25 mg fingolimod switch group (n=174)	Continuous 0·5 mg fingolimod (n=356)	Continuous 1·25 mg fingolimod (n=330)
Age (years)	36·1 (8·6)	36·1 (8·1)	36·5 (8·7)	35·5 (8·4)
Number of women	109 (65%)	114 (66%)	235 (66%)	227 (69%)
First multiple sclerosis symptom to randomisation (years)	7·6 (6·5)	7·0 (6·2)	7·3 (6·2)	6·9 (5·8)
Relapses in 1 year before enrolment	1·4 (0·7)	1·4 (0·8)	1·5 (1·3)	1·5 (0·9)
Relapses in previous 2 years	2·2 (1·0)	2·2 (1·2)	2·3 (2·3)	2·2 (1·2)
EDSS score	2·2 (1·2)	2·2 (1·2)	2·2 (1·3)	2·2 (1·3)
Multiple sclerosis treatment history (any treatment)	94 (56%)	98 (56%)	202 (57%)	190 (58%)
Number of gadolinium-enhancing lesions per patient on T1-weighted images	1·0 (2·5)	1·0 (3·1)	1·0 (3·0)	1·5 (4·9)
Volume of lesions on T2-weighted images (mm^3)	4791 (5172)	4521 (5442)	5181 (6929)	4963 (5750)
Normalised brain volume (cm^3)	1527 (73·6)	1529 (77·2)	1524 (82·8)	1532 (73·1)

Data are mean (SD) unless otherwise stated. EDSS=expanded disability status scale. ITT=intention to treat.

Table 1: **Baseline demographics and clinical characteristics at entry to the core study (extension ITT population)**

heart, lung, or liver disease; diabetes mellitus; previous total lymphoid irradiation; bone marrow transplantation; or cladribine, cyclophosphamide, mitoxantrone, or other immunosuppressant or monoclonal antibody treatment within 6 months.[1] We did not exclude patients if they had received previous treatment with interferon beta or glatiramer acetate. All patients who completed the core study on study drug were eligible to enter our extension phase.

All patients gave written informed consent for the core phase and separately for the extension phase. Our protocol was reviewed and approved by the Human Subjects Committees for each centre. The study methods were published previously[1] in accordance with CONSORT guidelines. The study adhered to the International Conference on Harmonisation Guidelines for Good Clinical Practice[5] and was done in accordance with the Declaration of Helsinki.[6]

Procedure

In the core study, patients were randomly assigned to receive, with equal probability, 0·5 mg daily oral fingolimod, 1·25 mg daily oral fingolimod, or 30 μg weekly intramuscular interferon beta-1a.[1] In the extension phase, patients who had received interferon beta-1a during the core phase were reassigned to receive either 0·5 mg or 1·25 mg once-daily fingolimod at a 1:1 ratio, and patients who had received fingolimod during the core phase continued on the same assigned dose in accordance with our protocol. Randomisation for the core study and re-randomisation for the extension study was done centrally in blocks of six within each site and was stratified according to site. Study group assignments were done with an interactive voice response system (IVRS). A randomisation list was produced by the IVRS provider with a validated system that automated the random assignment of patient numbers to randomisation numbers. These randomisation numbers were linked to the different treatment groups, which in turn were linked to medication numbers. A separate medication randomisation list was produced by Novartis Drug Supply Management with a validated system that automated the random assignment of medication numbers to medication packs containing each of the study drugs.

For patients entering our extension phase, the study site contacted the IVRS to change the status of the patient to completed at the end of the core phase (visit 11, month 12) once the last dose of core-phase study drug was given, and at this visit patients who had received interferon beta-1a during the core phase were reassigned. During the core study, treatment assignment and leucocyte counts were masked from patients, study personnel, MRI assessors, steering committee members, and the study statistician.[1] Capsules, syringes, and dispensable materials for active and control treatments were indistinguishable. Patients were instructed to cover injection sites at visits and not to discuss adverse events with clinical assessors. An independent data and safety monitoring board monitored safety in the overall phase 3 programme. During our extension, patients and investigators were aware that all patients were receiving fingolimod but the dose remained masked; doses for patients assigned to receive fingolimod in the core study were unmasked to Novartis personnel, but reassignment remained masked for those patients who were randomly reassigned to receive 0·5 mg or 1·25 mg fingolimod after receiving interferon beta-1a for the first year.

Annualised relapse rate (ARR) was defined as the total number of confirmed relapses for all patients in the treatment group, divided by the total number of days in the study for all patients in that group, multiplied by 365·25. EDSS and multiple sclerosis functional composite (MSFC) scores were recorded every 3 months and every 6 months, respectively. A relapse was defined as new, worsening, or recurrent neurological symptoms that occurred at least 30 days after the onset of a preceding

	Interferon beta-1a to fingolimod switch groups		Continuous fingolimod treatment groups	
	Interferon beta-1a to 0·5 mg fingolimod (n=167)	Interferon beta-1a to 1·25 mg fingolimod (n=174)	0·5 mg fingolimod (n=356)	1·25 mg fingolimod (n=330)
Clinical outcomes				
Total number of confirmed relapses				
Year before enrolment	234	244	534	495
Months 0–12	80	70	71	78
Months 13–24	52	41	65	55
Estimated annualised relapse rate (95% CI)				
Months 0–12	0·31 (0·22–0·43)	0·29 (0·20–0·40)	0·12 (0·08–0·17)	0·15 (0·10–0·21)
Months 13–24	0·22 (0·15–0·31)	0·18 (0·12–0·27)	0·11 (0·08–0·16)	0·11 (0·08–0·16)
p value*	0·049	0·024	0·80	0·12
Patients with no confirmed relapses				
Months 0–12	113 (68%)	122 (70%)	298 (84%)	267 (81%)
Months 13–24	128 (77%)	142 (82%)	305 (86%)	283 (86%)
p value†	0·040	0·007	0·49	0·08
MRI outcomes‡				
Number of new or enlarged T2 lesions				
Patients with evaluable scans at all timepoints	130	138	305	268
Months 0–12	2·1 (3·98), 1·0 (0–23)	2·4 (4·31), 1·0 (0–29)	1·6 (3·60), 0 (0–23)	1·4 (2·37), 1·0 (0–18)
Months 13–24	0·7 (1·54), 0 (0–10)	1·0 (1·87), 0 (0–13)	0·9 (1·65), 0 (0–15)	1·0 (2·3), 0 (0–19)
p value§	<0·0001	<0·0001	0·0001	0·0003
Patients without new or enlarged T2 lesions				
Months 0–12	64 (49%)	57 (41%)	171 (56%)	125 (47%)
Months 13–24	86 (66%)	82 (59%)	186 (61%)	162 (60%)
p value†	0·002	0·002	0·16	0·0005
Percent change in total volume (mm^3) of T2 lesions at month 24 *vs* month 12				
Patients with evaluable scans at all timepoints	128	136	305	266
mean (SD), median	−5·3 (33·9), −3·9	−6·0 (48·3), 1·2	−4·6 (45·2), −2·7	12·1 (142·8), 1·5
p value§	0·053	0·52	0·10	0·16
Number of Gd-enhancing lesions on T1-weighted images				
Patients with evaluable scans at all timepoints	124	134	289	262
Month 12	0·5 (1·62), 0 (0–10)	0·3 (0·83), 0 (0–6)	0·2 (0·75), 0 (0–6)	0·1 (0·49), 0 (0–6)
Month 24	0·1 (0·34), 0 (0–2)	0·2 (1·11), 0 (0–12)	0·1 (0·44), 0 (0–4)	0·2 (0·96), 0 (0–12)
p value§	0·002	0·011	0·64	0·25
Patients without Gd-enhancing T1 lesions				
Months 0–12	101 (82%)	111 (83%)	266 (92%)	241 (92%)
Months 13–24	111 (90%)	125 (93%)	261 (90%)	235 (90%)
p value†	0·052	0·013	0·46	0·35
Percent change in total volume (mm^3) of hypointense lesions on T1-weighted images at month 24 *vs* month 12				
Patients with evaluable scans at all time-points	112	113	259	231
mean (SD), median	−13·7 (89·0), −6·5	−2·5 (91·7), 3·6	−16·6 (164·2), −3·4	−23·3 (135·4), −2·7
p value§	0·054	0·63	0·002	0·06

Data are mean (SD), median (range) unless otherwise stated. Statistical analyses examined within groups comparisons between months 13–24 and months 0–12. *Months 13–24 versus months 0–12, negative binomial regression model (with repeated measures where treatment period is the main effect) adjusted for the number of relapses in 2 years before enrolment and baseline EDSS. †Months 13–24 versus months 0–12; exact McNemar's test. ‡Number (%) of patients excluded from the MRI analysis because they had received systemic steroid treatment within 30 days before MRI scan: interferon beta-1a to 0·5 mg fingolimod switch group, 4 (2%); interferon beta-1a to 1·25 mg fingolimod switch group, 5 (3%). §Months 13–24 versus months 0–12 (or month 24 *vs* month 12); Wilcoxon signed-rank test. ARR=annualised relapse rate. ITT=intention to treat. EDSS=expanded disability status scale.

Table 2: **Within-group comparisons (months 13–24 *vs* months 0–12) of clinical and MRI results (extension ITT population)**

relapse and lasted at least 24 h without fever or infection. A confirmed relapse was defined as accompanied by an increase of at least half a point on the EDSS, at least 1 point on two different functional systems of the EDSS, or at least 2 points on one of the functional systems (excluding bowel and bladder or cerebral functional systems). We included only confirmed relapses in our primary efficacy analysis.

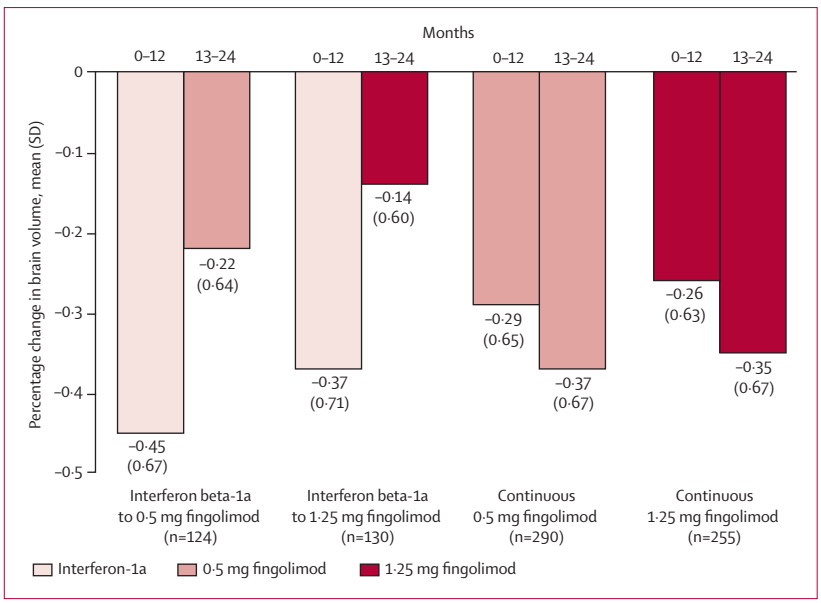

Figure 2: **Change in normalised brain volume during months 0–12 and months 13–24 in the extension ITT population**

Two-timepoint percentage brain volume change was estimated with the Structural Image Evaluation using Normalisation of Atrophy method. Within-group comparisons (months 13–24 *vs* months 0–12) were made with a Wilcoxon signed-rank test; p=0·006 for the interferon beta-1a to 0·5 mg fingolimod switch group and p=0·007 for the interferon beta-1a to 1·25 mg fingolimod switch group. Median percentage changes in brain volumes: interferon beta-1a to 0·5 mg fingolimod switch group months 0–12, –0·40% and months 13–24, –0·18%; interferon beta-1a to 1·25 mg fingolimod switch group months 0–12, –0·40% and months 13–24, –0·19%; continuous 0·5 mg fingolimod months 0–12, –0·20% and months 13–24, –0·30%; continuous 1·25 mg fingolimod months 0–12, 0·26% and months 13–24, –0·26%.

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At each site, a treating neurologist supervised medical management. A specially trained and certified examining neurologist established EDSS scores at scheduled and unscheduled visits. Confirmed disability progression required the change in EDSS to be present at a second visit 3 months later. Standardised MRI scans were obtained at screening, month 12, and month 24, or at study discontinuation and a 3-month follow-up visit, and were analysed centrally by the Image Analysis Center (Amsterdam, Netherlands). T1-weighted MRI scans after administration of the contrast medium 0·1 mmol/kg gadolinium diethylenetriamine pentaacetic acid (Gd), and T2-weighted scans were done to establish the effect of study drug on inflammatory disease activity. MRI scans done within 30 days of steroid treatment were excluded. Normalised brain volume was calculated at baseline and the percent change in brain volume was measured with Structural Image Evaluation using Normalisation of Atrophy (SIENA).[7] We did safety assessments at day 1, week 2, and months 1, 2, 3, 6, 9, and 12 of our extension phase.

Statistical analysis

We classified the data as core phase (months 0–12) or extension phase (months 13–24). We included all data up to month 24 on or before the database cutoff of Sept 30, 2009. With the exception of serious adverse events, we excluded safety data from more than 45 days after the permanent discontinuation of study drug.

Within-group analyses compared the effect of switching from interferon beta-1a to 0·5 mg or 1·25 mg fingolimod and were based on the extension intention-to-treat (eITT) and extension safety populations. The eITT and extension safety populations included all patients who entered the extension phase and received at least one dose of extension study drug. Between-group analyses compared the effect of continuous 0·5 mg or 1·25 mg fingolimod for 24 months with the interferon beta-1a to fingolimod switch group and were based on the core intention-to-treat (ITT) and core safety populations. The core ITT population included all patients who were randomly assigned to receive study drugs in the core study and received at least one dose of study drug, whereas the core safety population included all patients who received at least one dose of core study drugs. Our between-group analyses involving ARR and time-to-event endpoints used data from all patients in the core ITT population, whereas other efficacy analyses needed data for month 24 and thereby excluded patients without month 24 data. Similarly, our within-group efficacy analyses needed data for months 0–12 and months 13–24, and therefore excluded patients who withdrew from the core study or did not enter the extension phase, irrespective of their reasons for exit from the study. Further method and statistical modelling details are in the webappendix (pp 4–5) and the original report.[1] This study is registered with ClinicalTrials.gov, number NCT00340834.

Role of the funding source

The study was designed under the responsibility of Novartis Pharma AG in conjunction with the steering committee. Novartis collected and analysed the data, contributed to the interpretation of the study, and funded editorial assistance by Oxford PharmaGenesis. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

1123 (87%) of 1292 patients completed the core study on a study drug.[1] 1027 (92%) of the 1123 patients entered our extension and received study drugs, and 882 (86%) of these patients completed 24 months of treatment (figure 1). Baseline demographics and disease characteristics for the eITT population were similar across all treatment groups (table 1), and were consistent with those of the core ITT population.[1] Completion rates were slightly higher for patients who received continuous treatment with fingolimod (figure 1). The main reasons for discontinuation of treatment in the extension phase were withdrawal of consent (44 patients), adverse events (37), and abnormal laboratory values (36).

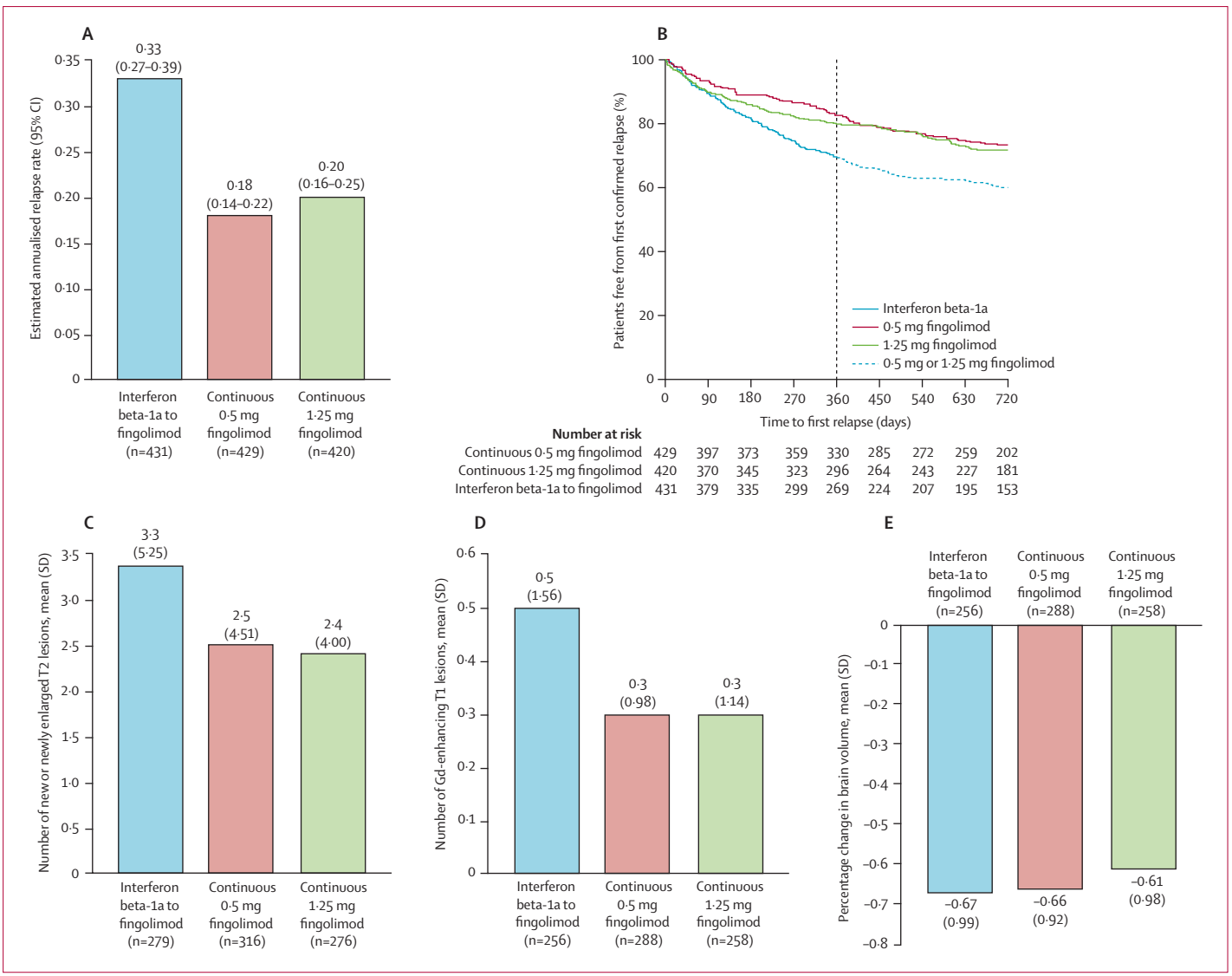

***Figure 3*: Clinical and MRI endpoints over 24 months, between-group comparisons from core ITT population**

(A) ARR, months 0–24, estimated from a negative binomial regression model adjusted for treatment, country, number of relapses in the 2 years before enrolment, and core baseline EDSS score. p<0·0001 for comparisons of estimated ARR in the continuous fingolimod treatment groups versus the interferon beta-1a to fingolimod switch group. (B) Time to first confirmed relapse with Kaplan–Meier estimate of patients free from relapse at 24 months. Survival distributions were compared via the log-rank test (p<0·0001 and p=0·0006 for the continuous 0·5 mg and 1·25 mg fingolimod groups, respectively, versus interferon beta-1a to fingolimod switch group). The hazard ratios (calculated from a Cox proportional hazard model adjusted by treatment, country, number of relapse in the previous 2 years before enrolment and core baseline EDSS) were 0·58 (95% CI 0·45–0·74) for the 0·5 mg fingolimod continuous treatment group versus the interferon beta-1a to fingolimod switch group and 0·64 (0·50–0·82) for the 1·25 mg fingolimod continuous treatment group versus the interferon beta-1a to fingolimod switch group. (C) Cumulative number of new or newly enlarged lesions on T2-weighted images up to month 24. p=0·035 for the between-group comparison of the number of lesions on T2-weighted images in the continuous 0·5 mg fingolimod group versus the interferon beta-1a to fingolimod switch group, done with a negative binomial regression model adjusted for treatment, core baseline volume of T2 lesions, and country (for continuous 1·25 mg fingolimod *vs* interferon beta-1a to fingolimod switch group, p=0·068). (D) Cumulative number of gadolinium-enhancing lesions on T1-weighted images over 24 months (the sum of month 12 and month 24 values). Between-group comparisons were made with a rank analysis of covariance (ANCOVA) adjusted for treatment, core baseline number of gadolinium-enhancing lesions on T1-weighted images, and country (continuous 0·5 mg fingolimod *vs* interferon beta-1a to fingolimod switch group). p=0·005 for the between-group comparison of the cumulative number of Gd-enhancing T1 lesions in both continuous fingolimod groups versus the interferon beta-1a to fingolimod switch group. (E) Percentage change in brain volume. Median changes: –0·60 for interferon beta-1a to fingolimod switch group, –0·50 for continuous 0·5 mg fingolimod, –0·50 for continuous 1·25 mg fingolimod. Number of patients excluded from the MRI analysis because they had received systemic steroid treatment within 30 days before MRI scan: 27 (6%) for continuous 0·5 mg fingolimod, 24 (6%) for continuous 1·25 mg fingolimod, 24 (6%) interferon beta-1a to fingolimod switch group. ARR=annualised relapse rate. EDSS=expanded disability status scale. Gd=gadolinium. ITT=intention to treat. For MRI outcomes, n=number of patients with evaluable scans at all time-points.

Patients who received interferon beta-1a in the core study (months 0–12) had relative reductions in ARR during months 13–24 of 30% after switching to 0·5 mg fingolimod (ARR ratio 0·70, 95% CI 0·49–1·00, p=0·049) and 36% after switching to 1·25 mg (0·64, 0·43–0·94, p=0·024; table 2). Significantly fewer patients had relapses after switching to fingolimod than during the previous year of treatment with interferon beta-1a (table 2).

	Interferon beta-1a to 0·5 mg fingolimod switch group (n=167)		Interferon beta-1a to 1·25 mg fingolimod switch group (n=174)	
	Months 0–12	Months 13–24	Months 0–12	Months 13–24
Any adverse event	152 (91%)	143 (86%)	163 (94%)	159 (91%)
Infectious adverse events	97 (58%)	91 (54%)	88 (51%)	91 (52%)
Most commonly reported adverse events*				
Influenza-like illness	71 (43%)	0	57 (33%)	7 (4%)
Nasopharyngitis	37 (22%)	37 (22%)	35 (20%)	35 (20%)
Headache	34 (20%)	26 (16%)	34 (20%)	25 (14%)
Pyrexia	27 (16%)	6 (4%)	30 (17%)	5 (3%)
Fatigue	16 (10%)	11 (7%)	22 (13%)	13 (8%)
Myalgia	14 (8%)	3 (2%)	22 (13%)	0
Depression	9 (5%)	5 (3%)	18 (10%)	7 (4%)
Lymphocyte count decreased	0	16 (10%)	0	19 (11%)
Lymphopenia†	0	20 (12%)	0	32 (18%)
Serious adverse event‡				
Any serious adverse event	10 (6%)	8 (5%)	8 (5%)	21 (12%)
Blood and lymphatic system disorders	0	1 (1%)	0	2 (1%)
Cardiac disorders	1 (1%)	1 (1%)	0	4 (2%)
Bradycardia	0	1 (1%)	0	2 (1%)
Second-degree atrioventricular block	0	0	0	2 (1%)§
Complete atrioventricular block	0	0	0	1 (1%)
Ear and labyrinth disorders	0	0	1 (1%)	2 (1%)
Eye disorders	0	1 (1%)	0	2 (1%)
Macular oedema	0	1 (1%)	0	2 (1%)
Gastrointestinal disorders	2 (1%)	0	1 (1%)	1 (1%)
Hepatobiliary disorders	1 (1%)	0	0	2 (1%)
Infections	3 (2%)	3 (2%)	1 (1%)	4 (2%)
Herpes zoster (disseminated and ophthalmic)	0	1 (1%)	0	1 (1%)
Neoplasms benign, malignant, unspecified (including cysts and polyps)	0	0	0	1 (1%)
Basal cell carcinoma	0	0	0	1 (1%)

*Adverse events reported in 10% of patients or more in either treatment group. †The study protocol was amended for the extension study (months 13–24) so that the criterion for lymphopenia was lymphocyte counts less than $0{\cdot}2\times10^9$/L, rather than less than $0{\cdot}1\times10^9$/L as for months 0–12; diagnosis of lymphopenia was established by the principal investigator. ‡List contains total number of serious adverse events and lists separately all those serious adverse events reported in two or more patients in any organ system class in either treatment group, all neoplasms, and adverse events of special interest. §Both cases were Mobitz type 1/Wenckebach second-degree atrioventricular block.

Table 3: **Adverse events and serious adverse events reported for patients switched from interferon beta-1a to fingolimod (extension safety population)**

MRI showed significant reductions in the cumulative number of new or newly enlarged T2 lesions after switching to 0·5 mg or 1·25 mg fingolimod and significant increases in proportions of patients without new or newly enlarged T2 lesions at month 24 compared with month 12 (table 2). The number of Gd-enhancing T1 lesions was also reduced versus the previous year of treatment with interferon beta-1a after switching to fingolimod (table 2). Compared with interferon beta-1a treatment in the core phase, the rate of brain volume decline was significantly reduced after the switch to 0·5 mg or 1·25 mg fingolimod (figure 2). Compared with interferon beta-1a treatment during year 1, after switching to fingolimod there were no significant changes in EDSS score (mean change –0·02 [SD 1·352] for switch to 0·5 mg fingolimod; 0·0 [1·276] for switch to 1·25 mg fingolimod) or MSFC *z*-score (mean change 0·037 [SD 0·901] for interferon beta-1a to 0·5 mg fingolimod; 0·002 [0·974] for interferon beta-1a to 1·25 mg fingolimod).

For those patients on continuous fingolimod treatment in the eITT population, benefits on clinical and MRI outcomes during the second year were either maintained (ARR, number of Gd-enhancing T1 lesions) or improved (cumulative number of new or enlarging T2 lesions). The rate of brain volume loss was similar in years 1 and 2 (figure 2).

Over 24 months, ARR was significantly reduced in the core ITT population by 46% (0·5 mg) and 39% (1·25 mg) in the continuous fingolimod groups compared with the interferon beta-1a to fingolimod switch group (ARR ratio 0·54 [95% CI 0·42–0·69] for 0·5 mg; 0·61 [0·48–0·78] for 1·25 mg; figure 3). 73% (95% CI 69–78%) of patients in the 0·5 mg

continuous fingolimod group (246 of 335), 71% (67–76%) in 1·25 mg continuous fingolimod group (203 of 284), and 60% (55–65%) switch group (163 of 273) did not have a relapse by 24 months, based on Kaplan–Meier estimates of relapse-free patients. A comparison of the survival curves suggests that fingolimod delays the onset of relapse (figure 3). The time to first 3-month confirmed disability progression did not differ between continuous fingolimod and switch groups.

In the continuous 0·5 mg fingolimod group, there were significantly fewer new or newly enlarged T2 lesions than in the switch group (figure 3) and more patients (134 [42%] of 316) were free from new or newly enlarged T2 lesions than in the switch group (93 [33%] of 279; p=0·016). The cumulative number of Gd-enhancing T1 lesions over 24 months (ie, the sum of months 12 and 24 values) was significantly lower in both continuous fingolimod groups than in the switch group (figure 3), and more patients were free from Gd-enhancing T1 lesions at months 12 and 24 combined in the 0·5 mg (259 [86%] of 300, p=0·001) and 1·25 mg (231 [86%] of 269, p=0·002) fingolimod groups than in the switch group (207 [77%] of 269). Over 2 years of treatment, the mean percentage brain volume change did not differ between the continuous fingolimod groups (figure 3). There was no significant difference in the change from baseline to month 24 in EDSS score (–0·01 [SD 0.94] for continuous 0·5 mg fingolimod; –0·08 [0·99] for continuous 1·25 mg fingolimod; 0·02 [0·89] for the interferon beta-1a to fingolimod switch group) or MSFC *z*-score (0·044 [0·4898] for continuous 0·5 mg fingolimod; 0·042 [0·5898] for continuous 1·25 mg fingolimod; 0·024 [0·4359] for the interferon beta-1a to fingolimod switch group).

Within the interferon beta-1a to 0·5 mg and 1·25 mg fingolimod switch groups in the extension safety population, the overall incidence of adverse events was slightly lower during treatment with fingolimod (months 13–24, 86% and 91%) than during treatment with interferon beta-1a (months 0–12, 91% and 94%; table 3). During the extension phase the pattern of adverse events shifted from one typical of interferon-1a (eg, influenza-like illness, pyrexia, fatigue, myalgia, and depression) to one typical of fingolimod (including abnormal hepatic enzyme levels, lymphopenia, and first-dose cardiac effects). Accordingly, the incidence of lymphopenia (table 3) and abnormal liver enzymes reported as adverse events rose after switching to fingolimod (abnormal liver enzymes: from 2% [three of 167 patients] to 10% [16 of 167] for interferon beta-1a to 0·5 mg fingolimod; from 1% [two of 174] to 14% [24 of 174] for interferon beta-1a to 1·25 mg fingolimod). Within both switch groups, overall infectious adverse events were similar before and after switching treatment. There was no association between the severity of lymphopenia and the incidence of infections.

Compared with the first year of treatment with interferon beta-1a, the incidence of serious adverse events was similar for patients switched to 0·5 mg fingolimod, but higher for patients switched to 1·25 mg fingolimod, during the second year (table 3). We recorded a rise in the incidence of serious cardiac-related adverse events after switching to 1·25 mg fingolimod (from 0% during the previous year of treatment with interferon beta-1a to 2%) but not to 0·5 mg fingolimod (stable at 1%; table 3). A complete atrioventricular block, lasting 30 s, was reported in one patient about 3 h after being given the first 1·25 mg fingolimod dose of the extension phase. The patient recovered spontaneously, was then treated with a single 0·125 mg intravenous dose of atropine, and recovered normal sinus rhythm within 24 h of onset of the event. The incidence of infections classed as serious adverse events was also increased compared with the previous year on interferon beta-1a after switching to 1·25 mg fingolimod (from 1% to 2%), but not to 0·5 mg fingolimod (stable at 2%). A single neoplasm and three cases of macular oedema were reported in patients after switching from treatment with interferon beta-1a to fingolimod (table 3). Severe events of increased hepatic enzymes were reported in two patients switched to 1·25 mg fingolimod and one patient switched to 0·5 mg fingolimod.

The proportions of patients who reported adverse events in the continuous fingolimod groups in the core safety population (webappendix pp 4–5) were lower in the extension phase (311 [72%] of 429 for 0·5 mg; 298 [71%] of 420 for 1·25 mg) than in the core phase (370 [86%] of 429 for 0·5 mg; 380 [90%] of 420 for 1·25 mg). During the second year of continuous fingolimod, nasopharyngitis (69 [16%] of 429 for 0·5 mg; 73 [17%] of 420 for 1·25 mg) and headache (49 [11%] of 429 for 0·5 mg; 36 [9%] of 420 for 1·25 mg) were the most common adverse events. The incidence of abnormal liver enzymes (detected by laboratory testing, not adverse event reporting) was lower during months 13–24 (6·1% for 0·5 mg; 8·8% for 1·25 mg) than during months 0–12 (13·3% for 0·5 mg; 11·0% for 1·25 mg) of continuous fingolimod. The incidence of lymphopenia reported as an adverse event during months 13–24 of continuous fingolimod (10·5% for 0·5 mg; 13·3% for 1·25 mg) was higher than during months 0–12 (0·2% for 0·5 mg; 1·0% for 1·25 mg). This increase coincided with a change in the lymphocyte count threshold that was the criterion for lymphopenia, from $0{\cdot}1\times10^9$/L to $0{\cdot}2\times10^9$/L. The mean change from baseline in lymphocyte count was similar at month 12 ($1{\cdot}779\times10^9$/L for continuous 0·5 mg fingolimod; $1{\cdot}766\times10^9$/L for continuous 1·25 mg fingolimod) and month 24 ($1{\cdot}756\times10^9$/L for continuous 0·5 mg fingolimod; $1{\cdot}802\times10^9$/L continuous 1·25 mg fingolimod).

The incidence of serious adverse events in the continuous fingolimod groups (webappendix pp 4–5) was reduced during months 13–24 compared with months 0–12 (4·4% *vs* 7·0% for 0·5 mg; 5·0% *vs* 10·5% for 1·25 mg). One patient in the continuous 1·25 mg fingolimod group

reported bradycardia on day 1 of the extension that resolved without treatment. The incidence of serious infections during the extension was low (0·7% for 0·5 mg; 1·6% for 1·25 mg) and did not differ with that recorded during months 0–12 (0·2% for 0·5 mg; 1·6% for 1·25 mg). Malignancies were reported in six patients who continued to receive fingolimod in our extension phase (four in the 0·5 mg group; two in the 1·25 mg group) compared with twelve during months 0–12 (eight in the 0·5 mg group; four in the 1·25 mg group). These malignancies consisted of four cases of localised skin cancers (basal cell carcinoma [0·5 mg], malignant melanoma in situ [1·25 mg], and two cases of squamous cell carcinoma [0·5 mg and 1·25 mg]), all of which were successfully excised, and one breast cancer (0·5 mg) and one ovarian epithelial cancer (0·5 mg). We did not identify an association between the malignancies and patient age; two patients older than 50 years had carcinomas. One case of macular oedema was reported in the second year of fingolimod therapy.

Panel: **Research in context**

Systematic review

A Pubmed search (up to April 2011 and without language restrictions) for "multiple sclerosis AND oral AND randomized AND (phase 3 OR phase III) AND interferon", confirmed that fingolimod is the only oral treatment for multiple sclerosis that has been investigated in a randomised, phase 3 clinical trial that includes an interferon active comparator.[1]

Interpretation

Fingolimod has previously shown superior efficacy to intramuscular interferon beta-1a on relapse and MRI outcomes in patients with relapsing-remitting multiple sclerosis. The findings of this extension study show that switching from interferon beta-1a treatment to fingolimod had beneficial effects with no unexpected safety concerns. These results also show that treatment outcomes are improved in patients treated continuously with fingolimod for 2 years compared with patients switched from interferon beta-1a to fingolimod.

Discussion

Our findings show that, in patients with RRMS, there were improvements in clinical and MRI measures of efficacy after switching from interferon beta-1a to fingolimod without the emergence of unexpected adverse events. Patients who received continuous fingolimod had reduced relapse rates and MRI lesion activity over 2 years relative to patients who received interferon beta-1a during the first year and fingolimod during the second year. We did not identify a loss of efficacy during months 13–24 for patients on continuous fingolimod, including findings of stable relapse rates and significantly reduced T2 lesion counts during months 13–24 compared with months 0–12. Our findings show that fingolimod was well tolerated during 2 years of treatment.

Our data complement the previously reported superiority of fingolimod compared with interferon beta-1a in the parallel-group TRANSFORMS core study[1] and show that fingolimod is efficacious in patients who have previously received interferon beta-1a (panel). After switching from interferon beta-1a to fingolimod, the pattern of adverse events changed from one typical of interferon beta-1a to one typical of fingolimod;[1,2,8–11] we did not record any unexpected adverse events after the switch to fingolimod.

Our findings from the continuous fingolimod groups show that clinical and MRI benefits of fingolimod were sustained to 24 months and are, therefore, consistent with those of FREEDOMS,[2] the 2-year, placebo-controlled study of 0·5 mg or 1·25 mg fingolimod. As in FREEDOMS, there were no clinically meaningful differences in the efficacy of 0·5 mg and 1·25 mg doses over 2 years of treatment. Improvements in efficacy outcomes in the continuous fingolimod groups compared with the interferon beta-1a to fingolimod switch group over 2 years suggest that a delay in the start of treatment with fingolimod, even while taking an active therapy, results in increased relapse rate and MRI lesion activity, although without effect on disability progression or change in brain volume. We expected this lack of difference on disability: during the core phase of the study, there was minimal disability progression, and the difference between treatment groups was only 1–2%. The absence of a statistically significant difference between years 1 and 2 in the continuous fingolimod groups suggest that the effect of fingolimod on brain atrophy was consistent over 2 years of treatment. We expected the recorded decrease in the rate of brain volume loss during treatment with fingolimod in year 2 compared with treatment with interferon beta-1a in year 1 in the within-group comparison, given the differences between the fingolimod and interferon beta-1a treatment groups in the core study,[1] and this result is consistent with clinical and MRI findings in year 2. That brain volume loss was numerically lower in patients switching to fingolimod during the extension than in patients who received continuous fingolimod might suggest an initial treatment-specific effect on brain volume, an effect of discontinuation of interferon treatment,[12] or both. These incompletely understood effects might explain the lack of a significant difference in the rate of brain volume loss in the between-group comparison of the switch and continuous-treatment groups over 24 months despite the difference recorded in the first year of this study and in both the first and second year of the FREEDOMS study.[2]

When given continuously for 2 years, fingolimod was well tolerated, and the safety profile was consistent with that reported previously.[1,2,8–11] The overall incidence of adverse events was lower during months 13–24 than months 0–12 for both continuous fingolimod doses, with adverse events associated with fingolimod (first-dose

cardiac effects, macular oedema, and raised hepatic enzyme titres)[1,2] predominantly in the first year of treatment. The increase in the incidence of lymphopenia reported as an adverse event during the second year of treatment with fingolimod was probably due to a change in the threshold for lymphopenia alerts during the extension, supported by similar mean changes from baseline in lymphocyte count for months 0–12 and months 0–24. The incidence of malignancies, including localised skin cancers, was generally lower during the extension phase than in the core study, suggesting that there was no increased cancer risk with increasing duration of treatment. The incidence of cardiac-related adverse events, serious infections, and macular oedema seemed to relate to dose, supporting a more positive benefit-to-risk ratio of the 0·5 mg dose (the approved dose) than the 1·25 mg dose.

A strength of our extension study is that we assessed the potential benefits and risks associated with switching patients from a first-line multiple sclerosis therapy to fingolimod. However, switching patients from the control treatment to fingolimod carries the inherent weaknesses of the absence of a placebo or active comparator control group—so the benefits recorded after switching cannot conclusively be shown to be solely due to fingolimod. It is also true that all patients were aware that they were receiving fingolimod. Furthermore, because our analyses required patients with data from both the core and extension phases, we excluded patients who withdrew from the core study or did not enter our extension phase. Consequently, our findings should be interpreted cautiously. It should also be noted that our conclusions are based on a large number of analyses with no adjustment for multiple comparisons. However, that our findings are consistent with both the 1-year TRANSFORMS core study and the 2-year, placebo-controlled FREEDOMS study lends credence to our results. Furthermore, our objective, quantifiable, and masked MRI lesion activity data support our clinical findings. We acknowledge that longer term follow-up in larger cohorts will be needed to better define benefits and risks.

Contributors

The steering committee (JC [chair], FB, GC, H-PH, LK, BK, XM, and JP) collaborated with the sponsor to design the study and monitor its conduct. All authors were involved in discussion and interpretation of the data and discussion and writing of the paper.

Conflicts of interest

BK (Bayer, Biogen Idec, Caridian, Novartis, Pfizer, Serono, Teva), FB (Bayer Schering Pharma, Biogen Idec, Janssen Research, Lundbeck, Merck Serono, Novartis, Roche, Sanofi-Aventis, Serono Symposia Foundation, Synthon BV, UCB), GC (Bayer Schering Pharma, Biogen Dompé, Merck Serono International, Novartis, Sanofi-Aventis, Serono Symposia International Foundation, Teva), H-PH (Bayer Healthcare, Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi-Aventis, Teva), LK (Actellion, Advancell, Allozyne, Barofold, Bayer Health Care Pharamceuticals, Bayer Schering Pharma, Bayhill, Biogen Idec, BioMarin, CLC Behring, Elan, Genmab, GeNeuro SA, Genmark, GlaxoSmithKline, Lilly, MediciNova, Merck Serono, Novartis, Novartis Research Foundation, Novonordisk, Peptimmune, Roche Research Foundation, Sanofi-Aventis, Santhera, Roche, Teva, UCB, Wyeth), XM (Bayer, Schering, Biogen Idec, EMD Merck Serono, Genentech, Genzyme, Novartis, Sanofi-Aventis, Teva), JP (Bayer Schering Pharma, Biogen Idec, Merck Serono, Novartis, Sanofi-Aventis, Teva), and JC (Biogen Idec, Elan, Lilly, Novartis, Serono, Synthon, Teva) have received payment for serving as consultants or speakers, or they or the institutions they work for have received research support from the companies indicated. FH, TS, SW, and LZ-A are or were employees of Novartis Pharmaceuticals Corporation or Novartis Pharma AG and hold stock or stock options in Novartis.

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