Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial

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Summary

Background Fingolimod has shown reductions in clinical and MRI disease activity in patients with relapsing-remitting multiple sclerosis. We further assessed the efficacy and safety of fingolimod in such patients.

Methods We did this placebo-controlled, double-blind phase 3 study predominantly in the USA (101 of 117 centres). Using a computer-generated sequence, we randomly allocated eligible patients—those aged 18–55 years with relapsing-remitting multiple sclerosis—to receive fingolimod 0·5 mg, fingolimod 1·25 mg, or placebo orally once daily (1:1:1; stratified by study centre). On Nov 12, 2009, all patients assigned to fingolimod 1·25 mg were switched to the 0·5 mg dose in a blinded manner after a review of data from other phase 3 trials and recommendation from the data and safety monitoring board, but were analysed as being in the 1·25 mg group in the primary outcome analysis. Our primary endpoint was annualised relapse rate at month 24, analysed by intention to treat. Secondary endpoints included percentage brain volume change (PBVC) from baseline and time-to-disability-progression confirmed at 3 months. This trial is registered with ClinicalTrilals.gov, number NCT00355134.

Findings Between June 30, 2006, and March 4, 2009, we enrolled and randomly allocated 1083 patients: 370 to fingolimod 1·25 mg, 358 to fingolimod 0·5 mg, and 355 to placebo. Mean annualised relapse rate was 0·40 (95% CI 0·34–0·48) in patients given placebo and 0·21 (0·17–0·25) in patients given fingolimod 0·5 mg: rate ratio 0·52 (95% CI 0·40–0·66; p<0·0001), corresponding to a reduction of 48% with fingolimod 0·5 mg versus placebo. Mean PBVC was –0·86 (SD 1·22) for fingolimod 0·5 mg versus –1·28 (1·50) for placebo (treatment difference –0·41, 95% CI –0·62 to –0·20; p=0·0002). We recorded no statistically significant between-group difference in confirmed disability progression (hazard rate 0·83 with fingolimod 0·5 mg *vs* placebo; 95% CI 0·61–1·12; p=0·227). Fingolimod 0·5 mg caused more of the following adverse events versus placebo: lymphopenia (27 [8%] patients *vs* 0 patients), increased alanine aminotransferase (29 [8%] *vs* six [2%]), herpes zoster infection (nine [3%] *vs* three [1%]), hypertension (32 [9%] *vs* 11 [3%]), first-dose bradycardia (five [1%] *vs* one [<0·5%]), and first-degree atrioventricular block (17 [5%] *vs* seven [2%]). 53 (15%) of 358 patients given fingolimod 0·5 mg and 45 (13%) of 355 patients given placebo had serious adverse events over 24 months, which included basal-cell carcinoma (ten [3%] patients *vs* two [1%] patients), macular oedema (three [1%] *vs* two [1%]), infections (11 [3%] *vs* four [1%]), and neoplasms (13 [4%] *vs* eight [2%]).

Interpretation Our findings expand knowledge of the safety profile of fingolimod and strengthen evidence for its beneficial effects on relapse rates in patients with relapsing-remitting multiple sclerosis. We saw no effect of fingolimod on disability progression. Our findings substantiate the beneficial profile of fingolimod as a disease-modifying agent in the management of patients with relapsing-remitting multiple sclerosis.

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Introduction

Fingolimod is an oral sphingosine-1-phosphate receptor modulator that inhibits egress of naive and central memory T cells from lymph nodes.[1] This inhibition results in fewer circulating lymphocytes and reduced cell trafficking to sites of tissue inflammation, including the CNS, which might account for its efficacy in multiple sclerosis.[1–4] Fingolimod is lipophilic and might also have secondary beneficial effects by targeting sphingosine-1-phosphate receptors on glia in the CNS.[1,5] In the phase 3 TRANSFORMS and FREEDOMS trials, fingolimod was more effective than the approved first-line treatment interferon β-1a[6] and placebo[7] in reducing both clinical and MRI outcome measures, including brain volume loss. In the FREEDOMS study, fingolimod also reduced disability progression compared with placebo at 24 months.[7] The drug is now approved as a once-daily oral treatment for relapsing forms of multiple sclerosis in more than 70 countries.

FREEDOMS II was a separate trial that started shortly after the pivotal phase 3 FREEDOMS and TRANSFORMS studies had started and was part of the global clinical development programme to investigate fingolimod in multiple sclerosis. The study conduct and analysis plan for these studies were developed in parallel. During development of fingolimod, the US Food and Drug

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Administration (FDA) requested several measurements not included in the first placebo-controlled trial (FREEDOMS), such as Holter monitoring. Novartis, the drug's manufacturer, therefore initiated the present trial, a second placebo-controlled phase 3 trial (FREEDOMS II), done predominantly in the USA and incorporating FDA requirements, to further assess the efficacy, safety, and tolerability of fingolimod in patients with relapsing-remitting multiple sclerosis treated for up to 24 months.

Methods

Study design and patients

FREEDOMS II was a 24-month, randomised, double-blind, placebo-controlled, parallel-group, multicentre study comparing the efficacy of once-daily fingolimod (0·5 mg and 1·25 mg doses) with placebo. Patients were enrolled in 117 academic and tertiary referral centres in eight participating countries, with most patients enrolled in the USA (101 centres; see appendix for a list of all countries). Patients were eligible for inclusion if they were aged 18–55 years, were diagnosed with relapsing-remitting multiple sclerosis according to the 2005 revised McDonald criteria,[8,9] had one or more confirmed relapses during the preceding year (or two or more confirmed relapses during the previous 2 years), had an Expanded Disability Status Scale (EDSS)[10] score of 0–5·5, and had no relapse or steroid treatment within 30 days before randomisation. Both treatment-naive and previously treated patients were included in the study; previously treated patients were eligible if interferon β or glatiramer acetate therapy was stopped at least 3 months before randomisation and natalizumab treatment at least 6 months before randomisation. Patients with clinically significant systemic disease or immune suppression (drug-induced or disease-induced), active infection or macular oedema, diabetes mellitus, or a history of malignancy (apart from successfully treated basal or squamous-cell skin carcinoma), and patients with specific cardiac, pulmonary, or hepatic disorders were excluded.

See Online for appendix

Each trial site obtained Institutional Review Board approval. The study was done in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. Patients provided written informed consent before participation. An independent data and safety monitoring board assessed the safety and overall benefit–risk profile during the trial.

Randomisation and masking

We randomly allocated patients (1:1:1; stratified by study centre) to receive oral fingolimod capsules in a dose of 0·5 mg or 1·25 mg or matching placebo, once daily for 24 months. The randomisation sequence was generated with an automated system under the supervision of the Novartis Drug Supply Management team. During the study, all study drugs dispensed to patients and all dosage changes were supplied by Novartis Drug Supply Management. To mask treatment allocation, both fingolimod and placebo were dispensed in hard gelatin capsules of identical colour and size and packed in identical bottles. The efficacy assessments (ie, confirmation of relapses, scheduled EDSS,[10] and Multiple Sclerosis Functional Composite [MSFC][11]) were done by an independent, specially trained, and certified assessor not otherwise involved in the treatment of patients (appendix). All MRI scans were centrally reviewed by an independent radiologist (E-WR) unaware of treatment allocation.

Procedures

The first patient in FREEDOMS II was enrolled on June 30, 2006, and the last assessment of the last patient was completed on June 24, 2011. After review of data from the FREEDOMS and TRANSFORMS phase 3 studies, completed on Nov 12, 2009, after consultation with and at the recommendation of the data and safety monitoring board, we decided to stop the 1·25 mg dose owing to the absence of clear added benefits and a higher risk for safety events such as infections and macular oedema (appendix). Patients on the high dose were subsequently switched to the 0·5 mg dose in a blinded manner. In December, 2010, after the regulatory approval of fingolimod 0·5 mg in the USA, the study was discontinued and all patients had the option to enrol in the open-label extension studies to receive fingolimod 0·5 mg.

Outcomes

Our primary objective was to show that fingolimod 0·5 mg per day is superior to placebo in reducing annualised relapse rates in patients with relapsing-remitting multiple sclerosis treated for up to 24 months (analysed by intention to treat). Only confirmed relapses were included for the efficacy analysis. A relapse was confirmed when it was accompanied by an increase of at least half a step (0·5) on the EDSS, an increase of 1 point on two different functional systems of the EDSS, or 2 points on one of the functional systems (excluding bowel, bladder, or cerebral functional systems). The key secondary objectives were to assess the effect of fingolimod 0·5 mg versus placebo on percent brain-volume change from baseline and time to disability progression (1 point EDSS change [0·5 point if baseline EDSS was >5·0]) confirmed at 3 months for up to 24 months. Other secondary objectives were to assess the following: safety and tolerability of fingolimod 0·5 mg compared with placebo; the time to first relapse and proportion of relapse-free patients; time to disability progression confirmed at 6 months, as measured by EDSS; change from baseline to the end of study on the MSFC score;[11,12] and effect on MRI measurements of inflammatory disease activity (number and volume of gadolinium-enhancing T1 lesions, number of new or newly enlarged T2 lesions, proportion of patients free of gadolinium-enhanced T1 lesions, proportion of patients free of new or newly enlarged

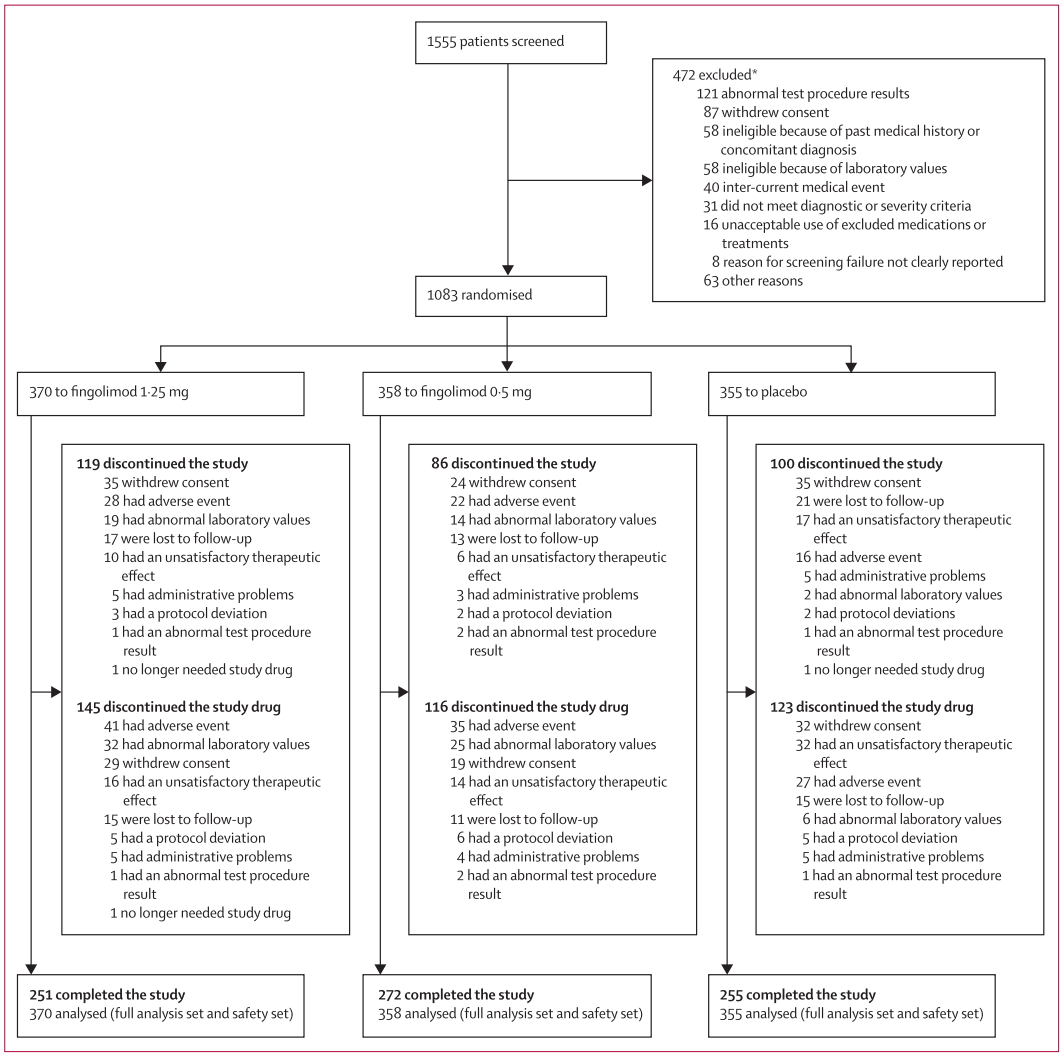

Figure 1: **Trial profile**
*Primary reason for screening failure (patients could have had more than one reason for screening failure).

T2 lesions, and proportion of patients free of new inflammatory activity [no gadolinium-enhanced T1 lesions and no new or newly enlarged T2 lesions]), and MRI measurements of burden of disease (percentage change from baseline in volume of gadolinium-enhanced T1 lesions, percentage change from baseline in volume of new or newly enlarged T2 lesions, and brain volume [at visits other than month 24]). We measured patients' quality of life using the Euro quality of life scale (EQ-5D) and Patient Reported Indices in Multiple Sclerosis (PRIMUS) instrument assessments; we measured fatigue using the Modified Fatigue Impact Scale (mFIS). All efficacy endpoints were prespecified in the study protocol. At the point at which patients were switched from 1·25 mg to the lower dose of fingolimod, 96 (85%) of 113 switched patients were on treatment with 1·25 mg for at least 360 days, and 64 (57%) were on the drug for at least 450 days. The mean time when the switch occurred was 518·8 days (SD 120·8).

We did extensive safety and tolerability assessments, in part as a response to preclinical safety concerns raised by the FDA and additional safety areas of interest identified in previous phase 2 and earlier clinical studies. We also recorded adverse events, serious adverse events, serious adverse events of special interest, 24 h Holter electrocardiography (ECG) post first-dose and at 3 months, first-dose bradycardia events, infections, laboratory tests, vital signs, ECG, echocardiography, pulmonary function

	Fingolimod 1·25mg (N=370)	Fingolimod 0·5 mg (N=358)	Placebo (N=355)
Age in years			
Mean (SD)	40·9 (8·9)	40·6 (8·4)	40·1 (8·4)
Median (range)	42·0 (18 to 57)	41·0 (18 to 55)	40·0 (19 to 55)
Number of women (%)	281 (76)	275 (77)	288 (81)
Body-mass index (kg/m^2)			
Mean (SD)	27·41 (5·956)	27·74 (5·952)	27·67 (6·458)
Median (range)	26·57 (16·7 to 45·9)	26·96 (13·9 to 50·8)	26·66 (16·9 to 56·6)
Disease and treatment history			
Years from first symptom to randomisation			
Mean (SD)	10·8 (8·2)	10·4 (8·0)	10·6 (7·9)
Median (range)	8·9 (0 to 50)	8·6 (0 to 49)	9·2 (0 to 40)
Number of relapses within previous year			
Mean (SD)	1·5 (1·0)	1·4 (0·9)	1·5 (0·9)
Median (range)	1·0 (0 to 12)	1·0 (0 to 6)	1·0 (0 to 7)
Number of relapses within previous 2 years			
Mean (SD)	2·3 (2·0)	2·2 (1·4)	2·2 (1·5)
Median (range)	2·0 (1 to 30)	2·0 (1 to 8)	2·0 (1 to 14)
EDSS score			
Mean (SD)	2·5 (1·3)	2·4 (1·3)	2·4 (1·3)
Median (range)	2·5 (0·0 to 6·0)	2·0 (0·0 to 6·5)	2·0 (0·0 to 6·0)
MSFC score			
Mean (SD)	0·0 (0·7)	0·04 (0·7)	−0·02 (0·8)
Median (range)	0·11 (−4·5 to 1·1)	0·18 (−2·7 to 2·1)	0·13 (−4·5 to 1·8)
Number of patients given previous treatment (%)	287 (78%)	264 (74%)	259 (73%)
Any interferon β	245 (66%)	218 (61%)	209 (59%)
Interferon β-1a (intramuscularly)	153 (41%)	129 (36%)	125 (35%)
Interferon β-1a (subcutaneously)	91 (25%)	91 (25%)	94 (27%)
Interferon β-1b (subcutaneously)	90 (24%)	73 (20%)	76 (21%)
Glatiramer acetate	169 (46%)	129 (36%)	146 (41%)
Natalizumab	23 (6%)	17 (5%)	23 (7%)
MRI disease characteristics*			
Number of patients without gadolinium-enhancing lesions on T1-weighted images (%)	254/367 (69%)	218/357 (61%)	225/354 (64%)
Number of gadolinium-enhancing lesions on T1-weighted images			
Mean (SD)	1·3 (3·6)	1·3 (3·4)	1·2 (3·2)
Median (range)	0 (0 to 26)	0 (0 to 33)	0 (0 to 46)
Total volume of gadolinium-enhancing lesions on T1-weighted images (mm^3)			
Mean (SD)	103 (299)	144 (448)	107 (307)
Median (range)	0 (0 to 3162)	0 (0 to 5570)	0 (0 to 4060)
Total volume of lesions on T2-weighted images (mm^3)			
Mean (SD)	4936 (7286)	5484 (8000)	5553 (7841)
Median (range)	2123 (0 to 55 257)	2356 (0 to 54 369)	2702 (0 to 69 203)
Total volume of hypointense lesions on T1-weighted images (mm^3)			
Mean (SD)	1144 (2312)	1417 (3011)	1434 (2732)
Median (range)	273 (0 to 19 431)	343 (0 to 23 937)	377 (0 to 17 362)
Normalised brain volume (cm^3)			
Mean (SD)	1518 (79)	1522 (82)	1526 (85)
Median (range)	1520 (1321 to 1741)	1530 (1285 to 1721)	1532 (1253 to 1756)

MSFC=Multiple Sclerosis Functional Composite. EDSS=Expanded Disability Status Scale. *MRI data are for patients with assessable scans at baseline.

Table 1: **Baseline demographic and clinical characteristics**

tests, chest high-resolution CT, chest radiographs, ophthalmic examinations, including serial optical coherence tomography, and dermatological assessments. Details of the study assessment procedure and schedule are given in the appendix.

Statistical analysis

We planned a sample size of 1080 randomised patients—ie, about 360 patients per arm. This sample size had a 93% power at the two-sided significance level of 0·05 to detect a relative annualised relapse rate reduction of 40% or more (assuming a 1·06 SD) and had a 90% power at two-sided significance level of 0·05 to detect an absolute difference of 12% in disability progression between the fingolimod 0·5 mg and placebo groups (assuming a 30% disability progression in the placebo group and a common dropout rate for the whole sample size of 25%). The primary endpoint was analysed by intention-to-treat analysis. We compared annualised relapse rates using a negative binomial regression model adjusted for treatment, region, number of relapses within 2 years before randomisation, and baseline EDSS score. We analysed the proportion of patients free of relapses using logistic regression adjusted for the same four variables as for the primary analysis. We compared brain volume, T2 lesion volume, and T1 lesion number and volume using rank ANCOVA adjusted for treatment, region, and baseline measurements. We analysed the number of new or newly enlarging T2 lesions using negative binomial and rank ANCOVA and analysed the proportion of patients free of lesions using a logistic

	Fingolimod 1·25 mg (N=370)	Fingolimod 0·5 mg (N=358)	Placebo (N=355)	Two-sided p value	
				Fingolimod 1·25 mg *vs* placebo	Fingolimod 0·5 mg *vs* placebo
Primary endpoint: annualised relapse rate (95% CI)	0·20 (0·17 to 0·25)	0·21 (0·17 to 0·25)	0·40 (0·34 to 0·48)	..	..
Rate ratio for fingolimod *vs* placebo (95% CI)	0·50 (0·39 to 0·65)	0·52 (0·40 to 0·66)	..	<0·0001	<0·0001
Percentage change in brain volume from baseline to month 24					
Number of patients with data	247	266	249	..	..
Mean (SD)	−0·595% (1·390)	−0·858% (1·222)	−1·279% (1·503)	..	..
Median (range)	−0·500% (−7·24 to 4·34)	−0·710% (−5·21 to 2·10)	−1·020% (−6·61 to 3·83)	..	..
Treatment difference *vs* placebo (95% CI)	−0·63% (−0·86 to −0·42)	−0·41% (−0·62 to −0·2)	..	<0·0001	0·0002
Percentage of patients without disability progression confirmed at 3 months (Mean [SE]) (95% CI)	78·3% (2·3) (73·7 to 82·9)	74·7% (2·5) (69·9 to 79·5)	71·0% (2·6) (65·9 to 76·1)	0·056	0·320
Hazard ratio for fingolimod *vs*placebo (95% CI)	0·72 (0·53 to 0·99)	0·83 (0·61 to 1·12)		0·041	0·227
Percentage of patients relapse free (mean [SE; 95% CI])	73·2% (2·5; 68·4 to 78·0)	71·5% (2·5; 66·6 to 76·4)	52·7% (2·8; 47·2 to 58·2)	<0·0001	<0·0001
Hazard ratio for fingolimod *vs* placebo (95% CI)	0·50 (0·38 to 0·64)	0·52 (0·40 to 0·67)	..	<0·0001	<0·0001
Percentage of patients free of disability progression, confirmed at 6 months (Mean [SE; 95% CI])	86·9% (1·9; 83·2 to 90·6)	86·2% (1·9; 82·3 to 90·0)	82·2% (2·2; 77·9 to 86·4)	..	..
Hazard ratio for fingolimod *vs* placebo (95% CI)	0·72 (0·48 to 1·08)	0·72 (0·48 to 1·07)	..	0·113	0·101
Change from baseline in EDSS score at month 24					
Mean (SD)	−0·084 (1·13)	0·046 (1·02)	0·055 (1·20)	0·190	0·945
Median	0·000	0·000	0·000	..	..
Change from baseline in MSFC score at month 24					
Mean (SD)	−0·08 (0·92)	0·00 (0·60)	−0·07 (0·54)	0·019	0·012
Median	0·03	0·06	−0·02	..	..
Measures of MRI inflammatory disease activity					
Number of new or newly enlarged T2 lesions, baseline to month 24*					
Number of patients with data	245	264	251	..	..
Mean (SD)	1·6 (5·41)	2·3 (7·26)	8·9 (13·86)	<0·0001	<0·0001
Median (range)	0·0 (0 to 63)	0·0 (0 to 97)	4·0 (0 to 109)	..	..
Patients free of T2 lesions at month-24 (n/N [%])	155/245 (63%)	133/264 (50%)	65/251 (26%)	<0·0001	<0·0001
Number of gadolinium-enhancing T1 lesions at month 24†					
Number of patients with data	251	269	256	..	..
Mean (SD)	0·2 (2·40)	0·4 (1·84)	1·2 (2·97)	<0·0001	<0·0001
Median (range)	0 (0 to 35)	0 (0 to 20)	0 (0 to 29)	..	..
Patients free of gadolinium-enhancing T1 lesions at month 24 (n/N [%])	242/251 (96%)	234/269 (87%)	167/256 (65%)	<0·0001	<0·0001
Patients free of new inflammatory activity at month 24—ie, no gadolinium-enhanced T1 lesions and no new or newly enlarged T2 lesions (n/N [%])	155/245 (63%)	133/264 (50%)	65/249 (26%)	<0·0001	<0·0001

(Table 2 continues on next page)

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