SUPPLEMENT

Methodological details and additional results not presented in the main text.

Assessments

Exploratory responders analysis

In this post hoc analysis, patients were classified based on presence (+) or absence (-) of clinical and MRI disease activity after 1 year of therapy (fingolimod or IFN β) for the following variables:

- Confirmed relapse (R+/R-): occurring during Year 1 on treatment
- 3-month confirmed disability progression (P+/P-): positive status defined as a one-point increase in the EDSS score
- MRI activity (MRI+/MRI-): positive status, if the sum of the number of new or newly enlarged T2 lesions at Month 12 compared with baseline and the number of Gd-enhanced T1 lesions at Month 12 was >2

Outcomes and time points

- No evidence of clinical disease activity status: defined as no relapses and no 6-month disability progression. Evaluated from the beginning of the Extension (M12) through the end of the study (EOS)
- No evidence of disease activity status: defined as no relapses, no 3-month disability progression and no MRI activity. Evaluated at the end of Year 1 in both the continuous fingolimod and IFN-switch groups and for the IFN-switch group alone at the end of Year 2, to assess the 12-month treatment effect with fingolimod following the switch from IFN

Results:

Supplement Table 1: Odds of being free of clinical disease activity* during extension phase (M13-EOS), by treatment, based on disease activity during core phase (M0-12)

Year 1 response groups	n	Odds ratios	95% CI	P-value
Continuous-fingolimod group (N=628)				
0 positives	398	1		
1 positive	180	0.63	(0.44, 0.90)	0.012
2 positives	48	0.35	(0.19, 0.64)	<0.001
3 positives	2	0.10	(0.00, 3.99)	0.218
IFN-switch group (N=296)				
0 positives	131	1		
1 positive	117	0.53	(0.32, 0.90)	0.018
2 positives	43	0.40	(0.20, 0.81)	0.011
3 positives	5	0.33	(0.05, 2.01)	0.228

1. Data was fit to a logistic regression model with Year 1 positive response count groups as a categorical predictor variable. Odds ratios, confidence intervals, and p-values are estimated using Firth's penalized likelihood method. Each group is compared with the 'No positives' group, which is used as a reference group.

2. The number of positives are counted in the Year 1 confirmed relapse/3-month confirmed disability progression/MRI activity response subgroups. For example, 3 positives is the R+/P+/MRI+ group. R=Confirmed relapse in Year 1; P=3-month confirmed disability progression in Year 1; MRI=MRI activity (# new/newly enlarged T2 lesions at Month 12 compared to baseline + # Gd+ T1 lesions at Month 12 > 2). +=Present; -=Absent.

* Clinical disease activity free status is defined as no confirmed relapses and no 6-month confirmed disability progression during Year 2 to end of study.

M, month; EOS, end of study; IFN, interferon

Supplement Table 2: Safety profile in the continuous-fingolimod 1.25 mg group and the IFN-switch 1.25 mg group

	Fingolimod 1.25 mg (N=330)	IFN-switch fingolimod 1.25 mg (N=174)
Adverse event, n (%) (at least 10% in either of the groups*)		
Overall AEs	312 (94.5)	168 (96.6)
Lymphopenia	117 (35.5)	66 (37.9)
Nasopharyngitis	105 (31.8)	53 (30.5)
Headache	51 (15.5)	36 (20.7)
Upper respiratory tract infection	47 (14.2)	28 (16.1)
Back pain	43 (13.0)	18 (10.3)
Urinary tract infection	40 (12.1)	10 (5.7)
Melanocytic nevus	37 (11.2)	16 (9.2)
Cough	32 (9.7)	22 (12.6)
Diarrhoea	28 (8.5)	20 (11.5)
ALT increased	25 (7.6)	19 (10.9)
SAE, n (%) (at least two patients in either of the groups*)		
Overall SAEs	40 (12.1)	37 (21.3)
Lymphopenia	1 (0.3)	2 (1.1)
Bradycardia	1 (0.3)	2 (1.1)
2nd degree AV block	0	2 (1.1)
Vertigo	2 (0.6)	2 (1.1)
Macular oedema	0	2 (1.1)
Herpes zoster	3 (0.9)	1 (0.6)
Pneumonia	3 (0.9)	0
Basal cell carcinoma	2 (0.6)	2 (1.1)
Multiple sclerosis relapse	4 (1.2)	0
Dyspnoea	2 (0.6)	0
Menorrhagia	0	2 (1.1)

*AE and SAE profile for the continuous fingolimod 0.5 mg and IFN-switch fingolimod 0.5 mg presented in the main manuscript.

AE, adverse event; ALT, alanine transaminase; IFN, interferon; SAE, serious adverse event.

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