Table e-1 Demographic and clinical characteristics at entry to FREEDOMS (extension ITT population subgroup of 48-month completers)

	Placebo to fingolimod switch groups		Continuous fingolimod treatment groups	
	Placebo–fingolimod 0.5 mg (n = 68)	**Placebo–fingolimod 1.25 mg[a] (n = 59)**	**Continuous fingolimod 0.5 mg (n = 155)**	**Continuous fingolimod 1.25 mg[a] (n = 126)**
Age, years	38.7 (8.4)	35.0 (9.7)	36.2 (9.1)	37.2 (8.8)
Female, n (%)	46 (67.6)	46 (78.0)	101 (65.2)	92 (73.0)
Time from first MS symptom to randomization, years	7.5 (5.7)	7.7 (6.6)	7.8 (6.6)	7.7 (5.7)
Number of relapses in 1year before enrollment	1.4 (0.6)	1.5 (1.0)	1.5 (0.8)	1.5 (0.9)

Number of relapses in 2 years before enrollment	2.0 (1.0)	2.3 (1.4)	2.2 (1.3)	2.2 (1.3)
EDSS score	2.5 (1.3)	2.5 (1.3)	2.4 (1.2)	2.3 (1.3)
Number of Gd-enhancing T1 lesions per patient	1.1 (2.7)	1.1 (2.0)	1.3 (3.4)	1.4 (3.1)
Volume of T2 lesions, mm^3	5796 (7157)	5460 (6197)	6263 (6769)	7174 (8445)
Normalized brain volume, mL	1513 (82.9)	1520 (88.6)	1520 (80.5)	1511 (93.3)

[a]All patients receiving fingolimod 1.25 mg/day were switched to fingolimod 0.5 mg/day after the 1.25 mg/day dose was discontinued from all MS clinical studies. Values are mean (standard deviation) unless otherwise stated.

Abbreviations: EDSS = Expanded Disability Status Scale. Gd = gadolinium. ITT = intent-to-treat. MS = multiple sclerosis.

Table e-2 Within-group comparisons (extension phase vs FREEDOMS) of ARRs and MRI outcomes during months 0–24 and months 24–48 (extension ITT population)

	Placebo–fingolimod 0.5 mg (n = 154)	Placebo–fingolimod 1.25 mg[a] (n = 145)	Continuous fingolimod 0.5 mg (n = 330)	Continuous fingolimod 1.25 mg[a] (n = 287)
ARR				
Months 0–24	0.42	0.37	0.21	0.12
Months 24–48	0.19	0.21	0.18	0.13
ARR estimate (95% CI)				
Months 0–24	0.42 (0.34–0.51)	0.36 (0.30–0.45)	0.20 (0.16–0.24)	0.12 (0.09–0.16)
Months 24–48	0.19 (0.13–0.26)	0.20 (0.15–0.27)	0.17 (0.13–0.22)	0.14 (0.10–0.18)
ARR ratio, month 24-48 vs month 0–24	0.45 (0.32–0.62)	0.55 (0.40–0.76)	0.85 (0.68–1.06)	1.14 (0.81–1.59)
p value, month 24-48 vs month 0–24	<0.0001	0.0003	0.1511	0.4487
NNT	4.33	6.10	33.33	58.82

Absolute risk reduction	0.23	0.16	0.03	−0.02
Number of Gd-enhancing T1 lesions				
Patients with evaluable MRI,[b] n	67	61	162	127
Month 24				
Mean (95% CI)	1.19 (0.96–1.49)	1.28 (1.02–1.60)	0.11 (0.07–0.18)	0.22 (0.15–0.32)
Median (IQR)	0 (0 to 1)	0 (0 to 2)	0 (0 to 0)	0 (0 to 0)
Range	0–17	0–9	0–5	0–11
Month 48				
Mean (95% CI)	0.07 (0.03–0.18)	0.11 (0.05–0.24)	0.30 (0.22–0.39)	0.23 (0.16–0.33)
Median (IQR)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Range	0–2	0–2	0–10	0–6
p value, month 24–48 vs month 0–24	<0.0001	<0.0001	0.0721	0.7326
Patients free from Gd-enhancing T1 lesions				
Patients with evaluable MRI,[c] n	75	69	171	137

Months 0–24, n (%)	24 (32.0)	22 (31.9)	128 (74.9)	110 (80.3)
Months 24–48, n (%)	60 (80.0)	54 (78.3)	136 (79.5)	106 (77.4)
p value, month 24–48 vs month 0–24	<0.0001	<0.0001	0.2682	0.5716
NNT	2.08	2.16	21.74	34.48
Absolute risk ratio	0.48	0.46	0.05	−0.03
Number of new or newly enlarged T2 lesions				
Patients with evaluable MRI, n	69	64	163	123
Months 0–24				
Mean (95% CI)	8.12 (7.47–8.82)	12.83 (11.98–13.74)	2.66 (2.42–2.93)	2.14 (1.89–2.41)
Median (IQR)	4 (1 to 11)	7.5 (1 to 16.5)	0 (0 to 2)	0 (0 to 2)
Range	0–59	0–99	0–107	0–40
Month 48				
Mean (95% CI)	1.43 (1.18–1.75)	2.34 (2.00–2.75)	2.58 (2.34–2.84)	1.71 (1.49–1.95)
Median (IQR)	0 (0 to 2)	0 (0 to 2)	0 (0 to 1)	0 (0 to 2)
Range	0–10	0–24	0–77	0–47

p value, months 24–48 vs months 0–24	<0.0001	<0.0001	0.0037	0.2491
Patients free from new or newly enlarged T2 lesions				
Patients with evaluable MRI[d]	69	65	163	126
Months 0–24, n (%)	16 (23.2)	12 (18.5)	82 (50.3)	67 (53.2)
Months 24–48, n (%)	38 (55.1)	34 (52.3)	113 (69.3)	72 (57.1)
p value, months 24–48 vs months 0–24	<0.0001	<0.0001	<0.0001	0.5515
NNT	3.13	2.96	5.26	25.64
Absolute risk reduction	0.32	0.34	0.19	0.04

ARR estimates based on a Poisson model (with repeated measures where treatment period is the main effect) adjusted for number of relapses in the 2 years before enrollment. Log (time in study) is the offset variable. Within-group comparisons (months 24–48 vs months 0–24) were made with the Wilcoxon signed-rank test. [a]All patients receiving fingolimod 1.25 mg/day were switched to fingolimod 0.5 mg/day after the 1.25 mg/day dose was discontinued from all MS clinical studies. [b]Number of patients with evaluable T1 MRI scans at both month 24 and month 48. cNumber of patients with evaluable T1 MRI scans. Includes patients not free of Gd-

enhancing T1 lesions at any time point, or free of Gd-enhancing T1 lesions at all time-points, in the specified periods being compared. [d]Number of patients with evaluable T2 MRI scans. Includes patients not free of T2 lesions at any timepoint, or free of T2 lesions at all timepoints, in the specified periods being compared. Abbreviations: ARR = annualized relapse rate. CI = confidence interval. Gd = gadolinium. IQR = interquartile range. ITT = intent-to-treat. MRI = magnetic resonance imaging. NNT = number needed to treat. SD = standard deviation.

Table e-3 Between-group comparison at month 24 of clinical and MRI outcomes during FREEDOMS, among patients who completed month 48 (FREEDOMS ITT population, subgroup of 48-month completers)

	Placebo group (switched to fingolimod in the extension) (n = 128)	Continuous fingolimod 0.5 mg (n = 156)	Continuous fingolimod 1.25 mg (n = 127)	*p* value for fingolimod 0.5 mg vs placebo	*p* value for fingolimod 1.25 mg vs placebo
ARR estimate (95% CI)					
Month 0–12[a]	0.36 (0.26, 0.50)	0.25 (0.18, 0.35)	0.08 (0.04, 0.15)	0.0964	<0.0001
NNT	–	9.26	3.56		
Absolute risk reduction	–	0.11	0.28		
Month 12–24[a]	0.33 (0.23, 0.45)	0.16 (0.11, 0.24)	0.07 (0.04, 0.14)	0.0041	<0.0001
NNT	–	6.21	3.95		
Absolute risk reduction	–	0.16	0.25		

Change in EDSS score, months 0–				0.1183	0.2469
24	128	155	125		
n[b]	0.04 (−0.13–0.20)	−0.06 (−0.20–0.07)	−0.02 (−0.16–0.12)		
Mean (95% CI)	0 (−0.5 to 0.5)	0 (−0.5 to 0)	0 (−0.5 to 0)		
Median (IQR)	−3.0 to 2.5	−3.0 to 3.0	−2.5 to 4.0		
Range					
Number of new or newly enlarged				<0.0001	<0.0001
T2 lesion, months 0–24					
n[b]	125	156	119		
Mean (95% CI)	9.63 (9.10–10.19)	2.67 (2.43–2.95)	1.76 (1.54–2.02)		
Median (IQR)	5.0 (1.0 to 14.0)	1.0 (0 to 2.0)	0 (0 to 2.0)		
Range	0 to 67	0 to 107	0 to 40		

Percentage change in T2 lesion volume, months 0– 24				<0.0001	<0.0001
n[b]	125	154	122		
Mean (95% CI)	28.40 (15.85–40.94)	7.39 (−0.66–15.45)	−1.31 (−5.15–2.53)		
Median (IQR)	7.87 (−3.53 to 33.03)	−1.19 (−10.39 to	−2.93 (−11.07 to		
Range	−40.9 to 525.2	7.55)	6.17)		
NNT	–	−100.0 to 299.6	−48.7 to 117.9		
Absolute risk reduction	–	4.76	3.37		
		0.21	0.29		
Number of Gd-enhancing T1 lesions at month 24				<0.0001	<0.0001
n[b]	119	152	122		
Mean (95% CI)	1.29 (1.11–1.52)	0.11 (0.07–0.18)	0.11 (0.06–0.18)		
Median (IQR)	0 (0 to 1)	0 (0 to 0)	0 (0 to 0)		
Range	0 to 17	0 to 5	0 to 6		

Percentage change in normalized brain volume, months 0–24				0.0048	0.0047
n[b]	119	147	119		
Mean (95% CI)	−1.41 (−1.68–−1.13)	−0.90 (−1.15–−0.66)	−0.89 (−1.13–−0.65)		
Median (IQR)	−1.17 (−1.87 to −0.37)	−0.70 (−1.45 to −0.20)	−0.63 (−1.68 to 0.08)		
Range	−7.00 to 1.38	−13.50 to 2.01	−5.42 to 1.74		

[a]ARRs are for confirmed relapses. ARRs and *p* values were estimated from a negative binomial regression model. [b]n = number of patients with data.

Abbreviations: ARR = annualized relapse rate. CI = confidence interval. EDSS = Expanded Disability Status Scale. Gd = gadolinium. IQR = interquartile range. MRI = magnetic resonance imaging. NC = not calculated. NNT = numbers needed to treat. SD = standard deviation.