Online-only supplementary appendix

This appendix has been provided by the authors to give readers additional information about their work.

Part I – eMethods

Definition of relapse and EDSS assessments

General definition of relapse: Appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event. The abnormality must be present for at least 24 hours and occur in the absence of fever (<37.5°C) or infection.

Definition of confirmed relapse: A relapse had to be confirmed by an EDSS certified physician. It was recommended that this had to occur within 7 days of the onset of symptoms. A relapse was confirmed when it was accompanied by an increase of at least half a step (0.5) on the EDSS or an increase of 1 point on two different Functional Systems (FS) of the EDSS or 2 points on one of the FS (excluding Bowel/Bladder or Cerebral FS).

EDSS assessments: For patients who previously participated in Phase 2/3 trials only, EDSS was assessed by a certified treating physician (all Phase 2/3 investigators and any new raters who joined during the study were required to provide one-time proof of Neurostatus EDSS certification). Physicians assessing EDSS for patients from Phase 3b trials did not have to be certified, and individual functional scores were not required.

Concomitant medications

The concomitant medications permitted for the management of potential adverse reactions associated with fingolimod included subcutaneous or intravenous administration of atropine up to 3 mg/day for symptomatic bradycardia as the first-line treatment, or a dopamine drip of 5–20 µg/kg/min or an epinephrine drip of 2–10 µg/min for nonresponsive bradycardia. A standard short course of intravenous methyl prednisolone 1000 mg/day for 3–5 days was recommended for relapses if clinically warranted; however, tapering was disallowed.

Statistical analysis

The safety analysis set included all patients who entered the LONGTERMS study and received at least one dose of fingolimod in any study, and excluded patients with major protocol deviations. The full analysis set included all patients who entered the LONGTERMS study and received at least one dose of fingolimod in any study and excluded those patients who were not included in the analysis during the core study due to protocol deviations.

Exploratory health outcomes

Health outcomes assessments included Patient Reported Indices in Multiple Sclerosis (PRIMUS) and Assessment of Multi-Dimensional Health Status EuroQoL (EQ-5D), Short Form Health Survey (SF-12) and Treatment Satisfaction Questionnaire for Medication (TSQM-9). These data were collected every 6 months only in patients who had completed these patient-reported outcomes (PROs) in their previous study.

PART II – eResults

Concomitant medication

Overall, 91.3% of patients required concomitant medications after starting fingolimod 0.5 mg in the LONGTERMS study, and the percentage decreased to 26.9% at the end of study (EoS) visit

after the last dose of fingolimod. Ibuprofen (22.7%), paracetamol (20.1%), methylprednisolone (10.8%) and methylprednisolone sodium succinate (8.0%) were the most routinely prescribed concomitant medications.

Discontinuations over a period of up to 14 years

Over a period of 14 years, 606 (14.8%) patients discontinued the study. From Year 1 to Year 4, the discontinuation rate was low (≤2.5%), and slightly increased between Year 5 and Year 9 (3.8%–5.2% annually), followed by further reduction at Year 10 (3.3%) and Year 12 (2.9%). Yearly discontinuation rates (4.0%) related to AEs showed a trend similar to the overall discontinuation rates (<1.0%) for most of the years, while rates increased by 1.2%, 1.4% and 1.4% for Years 5, 8 and 9, respectively. The study discontinuations at Year 12 were all due to AEs (n=3, 2.9%).

Post-hoc analysis of study 'late completers' (≥5 years) versus 'early completers' (<5 years)

Of the 3168 patients participating in the post-hoc analysis and receiving 0.5 mg fingolimod, 754 (84.2%; ≥5 years, n=895) and 2013 (88.6%; <5 years, n=2273) completed the study. For patients who received continuous fingolimod treatment for at least 5 years ('late completers'), the most common reasons for discontinuation of treatment when compared with the other group (<5 years, 'early completers') were AEs (4.1% vs. 3.2%), withdrawal of consent (3.7% vs. 2.4%) and unsatisfactory therapeutic effect of the treatment (3.5% vs. 1.8%).

Disease activity and severity at baseline was numerically higher in 'early completers' as opposed to 'late completers', as evidenced by higher EDSS scores T2 lesion burden (**eTable 1**). In addition, disease duration was longer in 'early' versus 'late completers' (**eTable 1**) and mean (SD) exposure to fingolimod was 466.4 (361.0) and 2860.1 (515.4) days, respectively.
At Year 5, the 'early completers' had a higher ARR than the 'late completers' (0.24 vs, 0.16, respectively) with fewer patients being relapse free (52.7% vs. 58.3%). The majority of the 'late completers' (69.2%) remained free from 6m-CDP at Year 8 compared with those in the 'early completers' group (40.5%). Change in T1 hypointense lesion volume followed a similar trend at the EoS.

Safety analyses revealed that lymphopenia (6.1% vs. 1.7%) and leukopenia (1.0% vs. 0.4%) were more commonly observed in early completers than late completers. Lymphopenia led to discontinuation of treatment in 0.6% of 'early completers' (n=14), but no discontinuations were recorded in the 'late completers'. Furthermore, nasopharyngitis (9.4% vs. 3.5%) and urinary tract infections (3.7% vs. 1.6%) were more commonly reported in early completers.

Laboratory abnormalities in hematology and blood chemistry values

As per **eTable 2**, a greater number of patients had clinically notable abnormal hematological parameters that included low lymphocytes ($<0.2\times10^9$/L), low leukocytes ($\leq2.0\times10^9$/L), low neutrophils ($\leq1\times10^9$/L) and low hemoglobin (≤100 g/L). Absolute lymphocyte counts decreased to $\leq0.05\times10^9$/L in four patients and to $\leq0.1\times10^9$/L in 120 patients during the study. Peripheral blood lymphocyte counts and total WBCs decreased from baseline to Month 24 (40.1% and 37.2%) and at the EoS (87.8% and 78.4%).

Hepatic enzyme elevations of 3- and 5-fold the upper limit of normal (ULN) were observed in patients for aspartate aminotransferase (AST; 68 [1.7%] and 14 [0.3%]) and alanine aminotransferase (ALT; 280 [6.9%] and 50 [1.2%]) levels. AST and ALT level elevations were

more frequent during early years of fingolimod treatment in the core studies. During the long-term study, three patients had elevated AST>10xULN, two had AST elevation >8xULN, six patients had ALT>10xULN, and four patients had ALT elevation >8xULN. For blood chemistry, notable abnormalities that occurred once during the study were for cholesterol (≥6.21 mmol/L), ALT (>90 U/L), triglycerides (≥3.39 mmol/L), AST (>82 U/L), total bilirubin (≥34.2 µmol/L) and glucose (≥11.11 mmol/L).

The percentage of patients with shifts in hematology and blood chemistry values from baseline to EoS is presented in **eTable 3.** As expected, given the mode of action of fingolimod, most shifts in hematology parameters were seen in the WBC parameters with shifts from normal at baseline to below normal range post baseline at Month 24 and EOS for lymphocytes (87.8% and 78.4%, respectively) and total WBC (40.1% and 37.2%, respectively). Blood chemistry shift analysis revealed that most marked shifts were observed in liver function tests (AST and ALT), where patients shifted from normal (baseline) to high values (post baseline). In addition, some patients with normal cholesterol (total) and triglycerides at baseline shifted to high levels during post-baseline visits.

Exploratory health outcomes

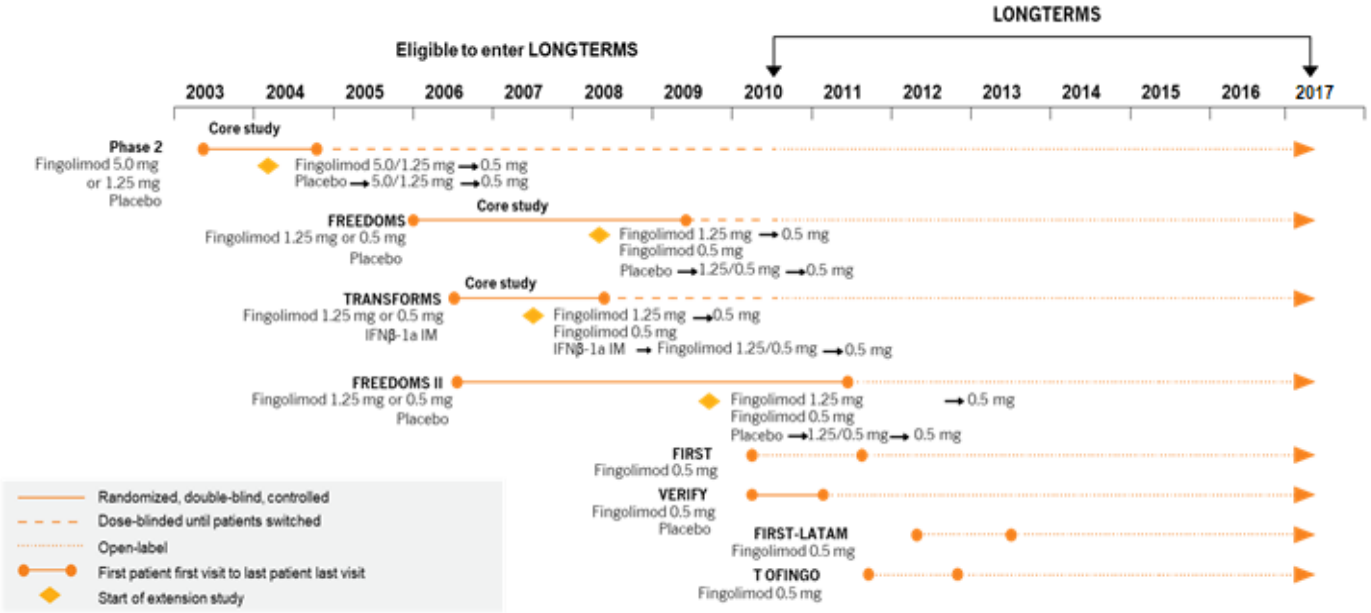
Due to the absence of a comparator arm in this open-label single-arm study, it was difficult to attribute any changes in respective PRO scores to a true treatment effect. The known variability in subsets of patients joining the long-term extension study from different core studies led to variation in administered PROs among the subsets of patients and a corresponding reduction in the group sizes, thus making it even more difficult to draw reliable conclusions.

During the long follow-up time in the study, mean changes in the PRIMUS-Activity total score increased while PRIMUS-QoL total score decreased from baseline. Mean changes in scores at Month 24 were 0.21 (PRIMUS-Activity) and −0.44 (PRIMUS-QoL), and at the EoS were 0.62 (PRIMUS-Activity) and −0.20 (PRIMUS-QoL).

Mean changes in EQ-5D utility scores slightly increased from baseline, i.e. −0.0020 (Month 24) and −0.0369 (EOS). The EQ-5D visual analog scale showed mean changes from baseline of 1.4 (Month 24) and −0.5 (EOS). The mean changes from baseline in summary scores of the SF-12 physical and mental components at Month 24 were 1.637 and −0.221, and 2.178 and 0.339 at the EoS, respectively. The TSQM-9 domain score remained stable between 74% and 79%. Overall, no clinically meaningful changes were reported for the health outcomes.

Part III – eFigure

eFigure 1. Patient flow in the LONGTERMS study from the previous core/extension studies



FIRST, Fingolimod Initiation and Cardiac Safety Trial; FIRST-LATAM, FIRST in Latin-American patients; FREEDOMS, FTY720 Research Evaluating Effects of Daily Oral therapy in MS; IFNβ-1a IM, intramuscular interferon β-1a; MS, multiple sclerosis; TOFINGO, Disease Control and Safety in Patients With RRMS Switching From Natalizumab to Fingolimod; TRANSFORMS, Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing–Remitting Multiple Sclerosis; VERIFY, Investigating the effect of recent immunization in patients receiving fingolimod therapy

Part IV – eTables

eTable 1. Demographics and baseline characteristics of patients treated with fingolimod 'any dose' in the overall population and in patients receiving '0.5 mg' for less than 5 years or for ≥5 years

	Fingolimod 'any dose' overall population (N=4086)	Fingolimod '0.5 mg' (N=3168)	
		≥5 year exposure (n=895)	<5 year exposure (n=2273)
Age, years			
Median (min–max)	38 (17–65)	37 (18–55)	38 (18–65)
Women, n (%)	2902 (71.0)	601 (67.2)	1655 (72.8)
Race, n (%)			
Caucasian	3892 (95.3)	840 (93.9)	2177 (95.8)
Black	35 (0.9)	9 (1.0)	13 (0.6)
Asian	35 (0.9)	10 (1.1)	19 (0.8)
Other	113 (2.8)	33 (3.7)	56 (2.5)
Native American	11 (0.3)	3 (0.3)	8 (0.4)
Duration of MS, years			
Since diagnosis			
Mean (SD)	5.9 (5.56)	4.8 (5.01)	6.7 (5.70)
Median (min–max)	4.4 (0–36.6)	3.0 (0–30.0)	5.3 (0–36.6)
Since first symptom			
Mean (SD)	8.7 (6.72)	7.9 (6.37)	9.3 (6.87)
Median (min–max)	7.2 (0.1–44.3)	6.4 (0.3–32.6)	7.7 (0.1–44.3)
MS relapses, mean (SD)			
Last 1 year	1.3 (1.01)	1.4 (1.00)	1.2 (1.04)
Last 2 years	2.1 (1.65)	2.2 (1.74)	2.1 (1.73)
EDSS score			
Mean (SD)	2.4 (1.43)	2.3 (1.26)	2.5 (1.54)
T2 lesion burden, mm^3			
Mean (SD)	6151.9 (7649.8)	5878.2 (7386.3)	7006.8 (8289.8)

eTable 2. Incidence of patients with notable lab abnormalities in hematology and blood chemistry (safety set)

Lab parameters	Notable criteria in SI units	Patients, n (%) (N=4086)
Hematology		
Hemoglobin	≤100 g/L	153 (3.7)
Platelets	≤100x10^9/L	47 (1.2)
(thrombocytes)	≥600x10^9/L	21 (0.5)
Leukocytes (WBCs)	≤2.0x10^9/L	437 (10.7)
	≥15x10^9/L	52 (1.3)
Neutrophils	≤1x10^9/L	160 (3.9)
	≥12x10^9/L	78 (1.9)
Lymphocytes	<0.2x10^9/L	814 (19.9)
	≥8x10^9/L	1 (<0.1)
Blood cells	<3.3x10^{12}/L	27 (0.7)
	>6.8x10^{12}/L	8 (0.2)
Blood chemistry		
SGOT (AST)	>82 U/L	193 (4.7)
SGPT (ALT)	>90 U/L	746 (18.3)
Total bilirubin	≥34.2 µmol/L	81 (2.0)
Alkaline phosphatase	>280 U/L	14 (0.3)
Cholesterol	≥6.21 mmol/L	1854 (45.4)
Triglycerides	≥3.39 mmol/L	571 (14.0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; WBC, white blood cells

eTable 3. Percentage of patients with shifts from baseline in hematology and blood chemistry values (safety set)

		Baseline			
Aspartate aminotransferase, n (%)					
Month 24		Low	Normal	High	Total
	Low	0	0	0	0
	Normal	0	1783 (91.7)	19 (1.0)	1802 (92.6)
	High	0	138 (7.1)	5 (0.3)	143 (7.4)
	Total	0	1921 (98.8)	24 (1.2)	1945 (100.0)
Month 48					
	Low	0	0	0	0
	Normal	0	1326 (94.0)	14 (1.0)	1340 (95.0)
	High	0	65 (4.6)	5 (0.4)	70 (5.0)
	Total	0	1391 (98.7)	19 (1.3)	1410 (100.0)
Month 96					
	Low	0	0	0	0
	Normal	0	459 (95.6)	5 (1.0)	464 (96.7)
	High	0	15 (3.1)	1 (0.2)	16 (3.3)
	Total	0	474 (98.8)	6 (1.3)	480 (100.0)
Month 120					
	Low	0	0	0	0
	Normal	0	89 (94.7)	2 (2.1)	91 (96.8)
	High	0	3 (3.2)	0	3 (3.2)
	Total	0	92 (97.9)	2 (2.1)	94 (100.0)
End of study					
	Low	0	0	0	0
	Normal	0	3562 (94.6)	35 (0.9)	3597 (95.5)
	High	0	161 (4.3)	8 (0.2)	169 (4.5)
	Total	0	3723 (98.9)	43 (1.1)	3766 (100.0)
		Baseline			
Alanine aminotransferase, n (%)					
Month 24		Low	Normal	High	Total
	Low	0	0	0	0
	Normal	0	1417 (72.7)	39 (2.0)	1456 (74.7)
	High	0	442 (22.7)	50 (2.6)	492 (25.3)
	Total	0	1859 (95.4)	89 (4.6)	1948 (100.0)
Month 48					
	Low	0	0	0	0
	Normal	0	1103 (78.1)	29 (2.1)	1132 (80.1)
	High	0	242 (17.1)	39 (2.8)	281 (9.9)
	Total	0	1345 (95.2)	68 (4.8)	1413 (100.0)
Month 96					
	Low	0	0	0	0
	Normal	0	396 (81.6)	15 (3.1)	411 (84.7)
	High	0	60 (12.4)	14 (2.9)	74 (15.3)

	Total	0	456 (94.0)	29 (6.0)	485 (100.0)
Month 120					
	Low	0	0	0	0
	Normal	0	81 (86.2)	3 (3.2)	84 (89.4)
	High	0	8 (8.5)	2 (2.1)	10 (10.6)
	Total	0	89 (94.7)	5 (5.3)	94 (100.0)
End of study					
	Low	0	0	0	0
	Normal	0	3090 (81.1)	87 (2.3)	3177 (83.4)
	High	0	562 (14.8)	70 (1.8)	632 (16.6)
	Total	0	3652 (95.9)	157 (4.1)	3809 (100.0)

Absolute lymphocytes, n (%)

		Baseline			
Month 24		Low	Normal	High	Total
	Low	50 (2.6)	1680 (87.8)	68 (3.6)	1798 (93.9)
	Normal	2 (0.1)	94 (4.9)	16 (0.8)	112 (5.9)
	High	0	1 (<0.1)	1 (<0.1)	2 (0.1)
	Total	52 (2.7)	1776 (92.8)	86 (4.5)	1914 (100.0)
Month 48					
	Low	38 (2.7)	1136 (82.2)	42 (3.0)	1216 (88.0)
	Normal	3 (0.2)	144 (10.4)	18 (1.3)	165 (11.9)
	High	0	1 (<0.1)	0	1 (<0.1)
	Total	41 (3.0)	1281 (92.7)	60 (4.3)	1382 (100.0)
Month 96					
	Low	18 (3.8)	368 (77.1)	10 (2.1)	396 (83.0)
	Normal	2 (0.4)	72 (15.1)	7 (1.5)	81 (17.0)
	High	0	0	0	0
	Total	20 (4.2)	440 (92.2)	17 (3.6)	477 (100.0)
Month 120					
	Low	9 (9.5)	68 (71.6)	2 (2.1)	79 (83.2)
	Normal	1 (1.1)	14 (14.7)	1 (1.1)	16 (16.8)
	High	0	0	0	0
	Total	10 (10.5)	82 (86.3)	3 (3.2)	95 (100.0)
End of study					
	Low	67 (1.8)	2938 (78.4)	89 (2.4)	3094 (82.6)
	Normal	7 (0.2)	583 (15.6)	59 (1.6)	649 (17.3)
	High	0	0	3 (<0.1)	3 (<0.1)
	Total	74 (2.0)	3521 (94.0)	151 (4.0)	3746 (100.0)

Absolute neutrophils, n (%)

		Baseline			
Month 24		Low	Normal	High	Total
	Low	38 (2.0)	301 (15.7)	2 (0.1)	341 (17.8)
	Normal	30 (1.6)	1475 (77.0)	36 (1.9)	1541 (80.4)
	High	0	26 (1.4)	8 (0.4)	34 (1.8)
	Total	68 (3.5)	1802 (94.1)	46 (2.4)	1916 (100.0)
Month 48					

	Low	10 (0.7)	83 (6.0)	1 (<0.1)	94 (6.8)
	Normal	34 (2.5)	1209 (87.4)	26 (1.9)	1269 (91.7)
	High	0	17 (1.2)	4 (0.3)	21 (1.5)
	Total	44 (3.2)	1309 (94.6)	31 (2.2)	1384 (100.0)
Month 96					
	Low	1 (0.2)	4 (0.8)	0	5 (1.0)
	Normal	10 (2.1)	443 (92.7)	9 (1.9)	462 (96.7)
	High	0	8 (1.7)	3 (0.6)	11 (2.3)
	Total	11 (2.3)	455 (95.2)	12 (2.5)	478 (100.0)
Month 120					
	Low	0	1 (1.1)	0	1 (1.1)
	Normal	0	90 (94.7)	1 (1.1)	91 (95.8)
	High	0	3 (3.2)	0	3 (3.2)
	Total	0	94 (98.9)	1 (1.1)	95 (100.0)
End of study					
	Low	20 (0.5)	60 (1.6)	0	80 (2.1)
	Normal	131 (3.5)	3392 (90.5)	68 (1.8)	3591 (95.8)
	High	0	67 (1.8)	10 (0.3)	77 (2.1)
	Total	151 (4.0)	3519 (93.9)	78 (2.1)	3748 (100.0)
Total white blood cells, n (%)					
			Baseline		
Month 24		Low	Normal	High	Total
	Low	27 (1.4)	774 (40.1)	4 (0.2)	805 (41.7)
	Normal	3 (0.2)	1050 (54.4)	55 (2.8)	1108 (57.4)
	High	0	8 (0.4)	8 (0.4)	16 (0.8)
	Total	30 (1.6)	1834 (95.0)	67 (3.5)	1931 (100.0)
Month 48					
	Low	15 (1.1)	513 (36.7)	5 (0.4)	533 (38.1)
	Normal	2 (0.1)	817 (58.4)	40 (2.9)	859 (61.4)
	High	0	6 (0.4)	1 (<0.1)	7 (0.5)
	Total	17 (1.2)	1336 (95.5)	46 (3.3)	1399 (100.0)
Month 96					
	Low	6 (1.2)	169 (34.9)	2 (0.4)	177 (36.6)
	Normal	0	287 (59.3)	16 (3.3)	303 (62.6)
	High	0	4 (0.8)	0	4 (0.8)
	Total	6 (1.2)	460 (95.0)	18 (3.7)	484 (100.0)
Month 120					
	Low	1 (1.1)	33 (34.7)	0	34 (35.8)
	Normal	1 (1.1)	56 (58.9)	3 (3.2)	60 (63.2)
	High	0	1 (1.1)	0	1 (1.1)
	Total	2 (2.1)	90 (94.7)	3 (3.2)	95 (100.0)
End of study					
	Low	47 (1.2)	1413 (37.2)	6 (0.2)	1466 (38.6)
	Normal	19 (0.5)	2181 (57.4)	104 (2.7)	2304 (60.6)
	High	0	24 (0.6)	6 (0.2)	30 (0.8)
	Total	66 (1.7)	3618 (95.2)	116 (3.1)	3800 (100.0)