

## Supplementary Appendix

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

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## APPENDIX

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## **ADDITIONAL METHODOLOGICAL DETAILS.**

### **Study Endpoints and Procedures**

In addition to the evaluations outlined in the main manuscript, ophthalmic examinations (including optical coherence tomography) and pulmonary function tests were performed at screening and months 1, 3, 6, and 12. Source documents for all suspected cases of macular edema were reviewed centrally by an independent retinal specialist. Skin examination was included in the general physical examination performed by the Treating Neurologist at Screening, and months 6 and 12. Following reports of skin malignancies in the fingolimod phase II study,<sup>1,2</sup> the protocol was amended to include regular dermatologic monitoring of all participants: monthly self-examination by participants and examination by a dermatologist at screening and month 12. All participants had been enrolled when this amendment was implemented, so the initial dermatologist examination occurred for all participants after dosing had commenced.

Relapses were treated with intravenous methylprednisolone up to 1000 mg/day for 3–5 days without an oral taper.

MR scans were acquired according to a standard protocol using 3 mm slices and included dual-echo T2-weighted and T1-weighted images before and after administration of single-dose gadolinium. Sites were required to successfully perform a dummy-run to optimize scan quality, and all subsequent scans had quality control performed by Perceptive Imaging who coded the images for central analysis by the Image Analysis Center in Amsterdam (Appendix) according to their Standard Operating Procedures.<sup>3</sup> New and enhancing lesions were identified by certified radiology reviewers, and their volumes determined by trained technicians using semi-quantitative software (Alice). Brain volume was measured with the Structural Image Evaluation Using Normalization of Atrophy (SIENA) program.<sup>4</sup>

The primary efficacy endpoint was annualized relapse rate, defined as the number of confirmed relapses over 12 months, and analyzed using a negative binomial regression model adjusted for treatment group, country, number of relapses in the 2 years before baseline, and baseline Expanded Disability Status Scale (EDSS) score, based on exploratory analyses of the phase II data and pre-specified in the protocol. The two key secondary endpoints were number of new or enlarged T2-hyperintense lesions at month 12 and time to confirmed disability progression. Disability progression was defined as a 1.0-point increase in EDSS score (0.5-point increase for baseline EDSS score  $\geq 5.5$ ), confirmed 3 months later in the absence of relapse. Secondary clinical endpoints also included time to first relapse, proportion of participants with confirmed disability progression, and changes in EDSS score and MS Functional Composite (MSFC) z-score from baseline to month 12. Secondary MRI endpoints included proportion of participants free from new or enlarged T2 or gadolinium-enhancing T1 lesions, and number and volume of gadolinium-enhancing T1 lesions. Additional MRI endpoints were changes from baseline in the volumes of T2 hyperintense and T1 hypointense lesions, and percentage change in brain volume.

### **Statistical Analysis**

The modified intent-to-treat cohort (n=1280), comprising all randomized participants who received at least 1 study drug dose, was the pre-specified primary efficacy analysis population. All participants were encouraged to continue on-study for follow-up assessments after discontinuation of study drug, and all data available for these participants, including data acquired after study drug discontinuation, were included in the analyses, i.e. relapses reported after study drug discontinuation were included. For participants who withdrew from the study prior to month 12, the number of relapses up to the time of discontinuation was used in the negative binomial regression model, and no imputation was applied for the time from study discontinuation to month 12. The per protocol population (n=1246) comprised all participants

without major protocol violations. Safety analyses were performed for the safety population (all participants who received at least 1 dose of study drug; n=1280) and were summarized using descriptive statistics without inferential significance testing.

Number of new or enlarged T2 lesions at month 12 was analyzed using a negative binomial regression model, adjusting for country, number of relapses in the 2 years before baseline, and baseline EDSS score. Time to confirmed disability progression was estimated using the Kaplan–Meier method and logistic regression model adjusting for baseline EDSS score and age. Cox’s proportional hazards model was used to model time-to-event and was adjusted for treatment, country, baseline EDSS score, and age. The proportions of relapse-free participants at month 12 (Kaplan–Meier estimates) were compared using a logistic regression model adjusting for country, number of relapses in the previous 2 years, and baseline EDSS score. Cox regression model was used to compare time to first relapse using the same covariates as the primary analysis. Changes in EDSS score and MSFC z-score from baseline were compared using Wilcoxon–Mann–Whitney rank-sum test and analysis of covariance on ranks. Other MRI endpoints were analyzed by non-parametric Wilcoxon–Mann–Whitney rank-sum tests and analysis of covariance on ranks model adjusting for treatment, country, and corresponding MRI baseline measurement for continuous and count variables, and a logistic regression model adjusting for treatment, country, and corresponding MRI baseline measurement for proportions.

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## HEMATOLOGY AND BLOOD CHEMISTRY RESULTS

		<b>Fingolimod 1.25 mg (N = 420)</b>	<b>Fingolimod 0.5 mg (N = 429)</b>	<b>IFNβ-1a (N = 431)</b>
White blood cell count (10 <sup>9</sup> /L)  Mean±SD	n	346	365	365
	Baseline	6.4±1.9	6.4±1.7	6.4±1.8
	Month 12	4.1±1.5	4.4±1.7	6.3±2.0
Neutrophil count (10 <sup>9</sup> /L)  Mean±SD	n	340	360	360
	Baseline	4.0±1.45	3.9±1.37	4.0±1.45
	Month 12	3.2±1.36	3.3±1.50	4.0±1.70
Lymphocyte count (10 <sup>9</sup> /L)  Mean±SD	n	339	359	359
	Baseline	1.8±0.53	1.8±0.53	1.7±0.52
	Month 12	0.4±0.26	0.5±0.31	1.7±0.57
ALC<0.8 x 10 <sup>9</sup> /L — no. (%) of participants		412 (98.1)	422 (98.4)	79 (18.3)
ALC<0.4 x 10 <sup>9</sup> /L — no. (%) of participants		349 (83.1)	308 (71.8)	11 (2.6)
ALC<0.2 x 10 <sup>9</sup> /L — no. (%) of participants		143 (34.0)	64 (14.9)	3 (0.7)
Bilirubin (µmoles/L)  Mean±SD	n	355	379	377
	Baseline	2.3±1.19	2.4±1.29	2.4±1.49
	Month 12	2.4±1.33	2.6±1.41	2.2±1.27
AST (U/L)	n	357	380	377

Mean±SD	Baseline	19.6±6.0	19.4±6.1	21.6±38.2
	Month 12	24.7±11.0	24.2±10.3	21.0±12.7
	% ≥3 x ULN	1.4%	2.1%	1.9%
ALT (U/L) Mean±SD	n	357	380	378
	Baseline	20.6±11.5	20.9±11.5	25.4±65.8
	Month 12	34.9±25.9	33.3±23.3	23.6±18.5
	% ≥3 x ULN	6.9%	8.4%	2.3%

ALC, absolute lymphocyte count; AST, aspartate transaminase; ALT, alanine transaminase; IFN, interferon; SD, standard deviation; ULN, upper limit of normal.