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The ACROSS study: Long-term efficacy of fingolimod in patients with relapsing–remitting multiple sclerosis

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Abstract

Background: In chronic diseases such as multiple sclerosis requiring lifelong treatment, studies on long-term outcomes are important.

Objective: To assess disability and magnetic resonance imaging-related outcomes in relapsing multiple sclerosis patients from a Phase 2 study of fingolimod 10 or more years after randomization and to compare outcomes in patients who had a higher fingolimod exposure versus those with a lower fingolimod exposure.

Methods: ACROSS was a cross-sectional follow-up study of patients originally enrolled in a Phase 2 fingolimod proof-of-concept study (NCT00333138). Disability and magnetic resonance imaging-related outcomes were assessed in patients grouped according to fingolimod treatment duration, based on an arbitrary cut-off: ≥8 years (high exposure) and <8 years (low exposure).

Results: Overall, 175/281 (62%) patients participated in ACROSS; 104 (59%) of these were classified "high exposure." At 10 years, patients in the high-exposure group had smaller increases in Expanded Disability Status Scale (+0.55 vs. +1.21), and lower frequencies of disability progression (34.7% vs. 56.1%), wheelchair use (4.8% vs. 16.9%), or transition to secondary progressive multiple sclerosis (9.6% vs. 22.5%) than those in the low-exposure group. The high-exposure patients also had less progression in most magnetic resonance imaging-related outcomes.

Conclusion: After 10 years of fingolimod treatment, disability progression was lower in the high-exposure group than in the low-exposure group.

Keywords: Relapsing–remitting multiple sclerosis, fingolimod, oral therapy, long-term treatment, ambulatory assistance, disability progression

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Introduction

The chronic and unpredictable nature of the multiple sclerosis (MS) disease course poses a great challenge for clinicians in routine clinical practice; monitoring long-term outcomes is therefore important for treatment optimization.[1,2] Observations in patients participating in pre-registration studies are particularly valuable because these patients are well characterized and, by definition, have a longer exposure to the drug than those who start treatment after marketing authorization. A systematic cross-sectional examination of as many as possible of the initial participants of a controlled study may provide valuable information about long-term outcomes.

Results from the 6-month controlled Phase 2 proof-of-concept study in patients with relapsing MS (NCT00333138) and its extensions over 1, 3, 5, and 7[3–6] years showed that fingolimod is associated with an early and sustained effect on disease activity.

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Three large Phase 3 clinical trials have established the superior efficacy of fingolimod over intramuscular interferon beta-1a (IFN β-1a)[7] or placebo[8,9] on clinical and magnetic resonance imaging (MRI)-related outcomes, including brain atrophy. However, continuous extension studies face increasing logistic and attrition problems with increasing duration. In the ACROSS study, we assessed clinical disability- and MRI-related outcomes in participants of the Phase 2 study of fingolimod 10 or more years after randomization.

Methods

Study design and patient population

In a 6-month, double-blind, placebo-controlled multi-center Phase 2 study, conducted from May 2003 to September 2004 (core study), the efficacy of fingolimod in patients with relapsing MS (McDonald criteria)[10] was evaluated.[3] ACROSS was a cross-sectional follow-up including patients originally enrolled in this Phase 2 study who had received ≥1 fingolimod dose (5.0 mg, 1.25 mg, or 0.5 mg) during the core study and its extensions, for a 10-year assessment regardless of their current treatment status.

After completing the Phase 2 extension studies, patients did not receive any protocol-specified treatment. Original Phase 2 study sites that agreed to participate in the ACROSS study located the study participants from their center and asked them to return for a 10-year assessment. As defined in the study protocol, based on the duration of fingolimod treatment, returning patients were divided into high and low exposure groups (i.e. those who had received fingolimod for 8 or more years and for fewer than 8 years, respectively). We selected this arbitrary cut-off based on precedence from an earlier long-term follow-up study.[11]

The study protocol was reviewed and approved by the Independent Ethics Committee and Institutional Review Board at each center as per local regulations. All patients provided written informed consent before study entry. The study was conducted in compliance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines.[12]

Primary assessment

The primary objective of the study was to assess whether high exposure to fingolimod (≥8 years) was associated with reduced disability progression, as measured by the mean change of the Expanded Disability Status Scale (EDSS) from baseline to 10 years, compared with low exposure. All EDSS scores were obtained by trained, certified assessors using the Neurostatus scoring tools for a standardized, quantified neurological examination. The tools for scoring and certification can be found online (www.neurostatus.net). For patients not able or willing to undergo the EDSS scoring in person, a validated EDSS phone interview was done.[13]

Secondary assessments

Disability outcomes. Secondary objectives included the proportion of patients with confirmed disability progression, the proportion of patients with an EDSS score <6, and the frequency and time to first required use of an ambulatory device or wheelchair. For patients under continuous care of the respective study centers, information about the time to event outcomes was extracted from history and file reviews and, where necessary, from other treating medical professionals. The proportion of patients with disability progression was defined as an increase in EDSS score by 1.5 (from baseline score 0), or 1 (from baseline score 1–5), or 0.5 (from baseline score >5). Paired comparison of the MS Functional Composite score (MSFC z-score) and its components (9-Hole Peg Test (9-HPT), Timed 25-Foot Walk Test (T25FWT), and Paced Auditory Serial Addition Test (PASAT-3)) were done for those patients with assessments at baseline and year 10.

Secondary progressive MS conversion. Conversion to secondary progressive MS (SPMS) was determined by the treating physician at the 10-year follow-up according to the Lublin and Reingold 1996 criteria.[14]

MRI assessment. A standard MRI protocol was acquired at year 10 for comparison with the baseline MRI of the Phase 2 study. The MRI protocol included axial two-dimensional (2D) T1-weighted (T1w) images (3 mm slice thickness, no gap) before and after administration of a contrast agent, and 2D dual-echo T2w images in an identical slice position.

T2w lesion load was quantified on proton density images at baseline and 10 years, following a highly standardized procedure by a central core lab specializing in analyses of Phase 3 clinical trials (Medical Image Analysis Center, Basel, Switzerland), and the number of new/enlarging

T2w lesions (i.e. lesions visible at 10 years, but not at baseline) were determined. T1w lesions were also segmented with the same protocol at baseline and at 10 years. Percentage brain volume change (PBVC) from core baseline to year 10 was also determined.

Safety. During the site visit, patients were asked to report on any adverse events (AEs) and their files were reviewed for such events. Further, a physical examination was done and vital signs were measured (data not presented).

Statistical analyses

The primary variable was analyzed using analysis of covariance (ANCOVA), where the change in the EDSS score from baseline to 10 years was the response variable and the baseline EDSS score was a continuous covariate, whereas fingolimod treatment duration (high vs. low exposure) was a fixed effect. A sensitivity analysis with fingolimod treatment duration as a continuous variable was also performed. Factors in the core phase predicting disability progression after 10 years were analyzed with change in the EDSS score from baseline to 10 years as the response variable and baseline characteristics such as gender, age, EDSS score, T2 lesion counts and volume, MSFC z-score, and fingolimod treatment duration (high vs. low exposure categories) as covariates. Adjusted least squares means (LSMs) and their corresponding standard errors were reported in addition to the adjusted mean differences and standard errors. Kaplan–Meier (KM) plots and hazard ratios (HRs) with 95% confidence interval (CIs) using a Cox proportional hazard model were reported for the first time use of an ambulatory device and wheelchair and for patients who transitioned to SPMS. The ANCOVA model was also used to analyze change in the volume of T2w lesions at 10 years.

Correlations between fingolimod treatment duration and MS disease outcomes (disability, conversion to SPMS and MRI lesions) were assessed using Pearson correlation coefficients.

Results

Patient disposition and baseline characteristics

Of the 32 centers that participated in the core Phase 2 study, 26 recruited patients for ACROSS; of note, all sites from Finland could not participate ($n = 20$ randomized patients from three centers). A total of 175 (62.3%) of the 281 patients originally randomized in the Phase 2 study participated in this 10-year follow-up, which accounted for an ascertainment rate of 84% in the participating sites (Supplementary Table 1). Overall, 104 (59.4%) and 71 (40.6%) patients were assigned to the high and low exposure groups, respectively. The 106 patients who did not participate in the cross-sectional follow-up did not differ from the 175 participating patients for age, race, or body weight at core baseline; however, there was a trend for female preponderance in non-participants ($p = 0.0605$). Non-participants had a similar disease duration but a higher EDSS score ($p = 0.0008$) and a trend for a higher T2 burden of disease ($p = 0.0575$) at core baseline (Table 1). The mean fingolimod exposure in the high exposure group was 4003 days, and 1190 days in the low exposure group. Details pertaining to the use of other disease-modifying therapies (DMTs) are provided in Supplementary Table 2. Significant differences in baseline characteristics between the groups were observed for the proportion of women ($p < 0.05$), mean EDSS scores ($p < 0.05$), and mean MS duration since the first symptom ($p < 0.02$; Table 2).

Disability outcomes

At 10-year follow-up, EDSS was assessed in 172 patients (by phone, $n = 5$). The mean EDSS scores in the overall population increased from baseline of core study by 0.83. EDSS increase was lower in the high exposure group compared to the low exposure group (LSM: 0.58 vs. 1.17; $p = 0.0155$; Table 3). In the sensitivity analysis, longer exposure to fingolimod significantly correlated ($p = 0.0143$) with a lower EDSS at 10 years. Furthermore, a significant correlation was observed between change in EDSS from baseline to 10 years and longer exposure to fingolimod treatment ($p = 0.0162$) as well as age at baseline ($p = 0.0116$); no correlations were observed with the other covariates (gender, EDSS score, T2 lesion counts and volume, MSFC z-score). Fewer patients experienced disability progression in the high exposure group than in the low exposure group at 10 years (34.7% vs. 56.1%; $p < 0.01$; Table 3). Overall, 144 of 172 (83.7%) patients had EDSS scores of <6 at 10 years, and this proportion was greater in the high exposure group than in the low exposure group (89.1% vs. 76.1%; $p < 0.05$). Mean (standard deviation (SD)) time to first use of an assistive device for ambulation was longer in the high exposure group compared with the low exposure group (8.3 (2.3) vs. 5.2 (3.1) years; Table 3). The absolute number of patients who needed an assistive device for ambulation were lower in the high exposure group (12/104 (11.5%) vs. 12/71

Table 1. Patient demographics and characteristics at baseline of the core study and in patients who participated, or did not participate, in ACROSS.

	ACROSS study participation			
	Yes	No	*p* value	Core study
Participants, *n* (%)	175 (62.3)	106 (37.7)		281 (100.0%)
Sex, *n* (%)				
Female	117 (66.9)	82 (77.4)	0.0605[a]	199 (70.8)
Age group, years, *n* (%)				
≤30	47 (26.9)	26 (24.5)	0.2150[b]	73 (26.0)
31–40	64 (36.6)	36 (34.0)		100 (35.6)
41–50	49 (28.0)	27 (25.5)		76 (27.0)
>50	15 (8.6)	17 (16.0)		32 (11.4)
Mean (SD) age, years	37.4 (9.3)	38.5 (10.1)	0.4292[c]	37.8 (9.6)
BMI, *n*	172	105		277
Mean, kg/m^2	24.45 (4.3)	24.37 (4.4)	0.7692[c]	24.42 (4.4)
Race, *n* (%)				
Caucasian	172 (98.3)	104 (98.1)	0.4061[a]	276 (98.2)
Black	2 (1.1)	0 (0.0)		2 (0.7)
Asian	1 (0.6)	0 (0.0)		1 (0.4)
Duration of MS since first symptom, years				
Mean (SD)	8.5 (7.8)	9.0 (7.5)	0.3477[c]	8.7 (7.6)
Median	6.7	7.9		7.0
Baseline EDSS				
Mean (SD)	2.3 (1.2)	3.0 (1.5)	0.0008[c]	2.6 (1.4)
Median	2.0	2.5		2.0
Mean baseline T2 lesion volume, mm^3	8584.4 (12,558.9)	10,598.9 (10,639.5)	0.0575[c]	9355.1 (11881.0)

[a]Chi-square test.
[b]Mantel Haenszel chi-square test.
[c]Wilcoxon rank sum test.
BMI: body mass index; EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; SD: standard deviation.

(16.9%); KM analysis also showed similar findings (Figure 1). The HR for the first time use of an assistive device for ambulation was 0.86 (95% CI: 0.37–2.01; relative risk reduction, 14%; $p = 0.7338$) by treatment group (high vs. low exposure groups).

Mean (SD) time to first use of a wheelchair was slightly longer in the high exposure group than in the low exposure group (7.2 (2.5) vs. 6.2 (2.5) years). The absolute numbers of patients who needed a wheelchair were lower in the high exposure group (5/104 vs. 12/71 for the low exposure group; Table 3). The corresponding KM curves are presented in Figure 2. In the high exposure group, the risk for need of a wheelchair was reduced by 76% versus low exposure group (HR (95% CI): 0.24 (0.07–0.85; $p = 0.0276$); Table 3). No patient in the ACROSS study was bedridden.

SPMS conversion

A total of 26 (14.9%) patients were classified as having SPMS at 10 years. A lower proportion of patients in the high exposure group transitioned to SPMS compared with the low exposure group (KM estimates: 8.1% vs. 18.2%; Table 3). Furthermore, mean (SD) time to first classification as SPMS was longer in the high versus low exposure group (5.4 (4.7) years vs. 3.4 (6.0) years; Table 3). In comparison to the low exposure group, the risk of developing SPMS was 66% lower in the high exposure group (HR (95% CI): 0.34 (0.12–0.92); $p < 0.05$; Table 3).

MSFC z-score

At core baseline, MSFC was assessed in 104 patients from the high exposure and 69 patients from the low exposure group. At follow-up, it was assessed in 89 and 51 patients, respectively. The change from core baseline in the MSFC z-score (mean (SD): −0.1

Table 2. Patient demographics and baseline characteristics of patients with high and low fingolimod exposure at entry into the core study.

	High exposure ($N = 104$)	Low exposure ($N = 71$)
Sex, *n* (%)		
Female*	63 (60.6)	54 (76.1)
Age group, years, *n* (%)		
≤30	25 (24.0)	22 (31.0)
31–40	42 (40.4)	22 (31.0)
41–50	31 (29.8)	18 (25.4)
>50	6 (5.8)	9 (12.7)
Age, years	37.4 (8.5)	37.4 (10.6)
BMI, *n*	102	70
Mean, kg/m^2	24.78 (4.1)	23.96 (4.7)
Race, *n* (%)		
Caucasian	103 (99.0)	69 (97.2)
Black	1 (1.0)	1 (1.4)
Asian	0 (0.0)	1 (1.4)
Duration of MS since first symptom, years*	7.4 (6.3)	10.1 (9.3)
Median	6.0	7.8
EDSS at baseline**	2.2 (1.2)	2.6 (1.2)
Median	2.0	2.0
T2 lesion volume at baseline,		
n	96	67
mm^3	7698.6 (8209.4)	9853.6 (16,951.7)

*$p < 0.05$ and **$p < 0.02$ between the treatment groups. All other values were not significantly different.
All values are represented as the mean (SD), unless otherwise specified.
BMI: body mass index; DMTs: disease-modifying therapies; EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; SD: standard deviation.

(0.5) vs. −0.6 (1.3); $p < 0.01$) and PASAT-3 score (0.5 (8.3) vs. −5.4 (12.4); $p < 0.001$) at year 10 was significantly in favor of the high exposure group. No significant differences between the two treatment groups were observed for the T25FWT (1.3 (11.6) vs. 3.9 (16.1)) or 9-HPT (2.3 (5.8) vs. 5.1 (14.5)) scores.

MRI outcomes

Total T2w lesion volume increased from baseline in both groups (Table 4). Mean increase in total T2w lesion volume was lower in the high exposure group compared to the low exposure group (LSM increase of 1031.5 mm^3 vs. 3636.9 mm^3; $p < 0.05$).

At 10 years, the number of new or enlarging T2w lesions was also significantly lower in the high exposure group than in the low exposure group (LSM: 10.7 vs. 22.2; $p < 0.0001$; Table 4). A lower T1w hypointense lesion volume was observed with high exposure (3357.6 mm^3) than with low exposure (4216.2 mm^3), although the difference did not reach significance.

The PBVC from core baseline at year 10 was significantly lower in the high exposure group than in the low exposure group (LSM: −9.20% vs. −10.01%).

Correlation analyses

Positive correlations were observed between the duration of fingolimod treatment and the time to first use of an ambulatory device ($r = 0.46$; $p = 0.0144$) whereas a negative correlation was observed with the EDSS score at year 10 ($r = -0.27$; $p = 0.0004$). No correlations were observed between the duration of fingolimod and other variables such as time to first use of a wheelchair ($r = 0.36$; $p = 0.1573$), time to first SPMS classification ($r = 0.31$; $p = 0.1222$), time to first documentation of an EDSS score of ≥6.0 ($r = 0.28$; $p = 0.1935$), changes in MRI measures from the Phase 2 baseline to the 10-year assessments, and with MRI parameters at 10 years.

Table 3. Disability outcomes at the 10-year follow-up.

	Fingolimod treatment duration	
	High exposure (N = 104)	Low exposure (N = 71)
Primary assessment		
EDSS change from the core study baseline to the 10-year follow-up		
Core baseline		
n	104	71
Mean (SD)	2.16 (1.2)	2.60 (1.2)
Year 10		
n	101	71
Mean (SD)	2.72 (1.9)	3.81 (2.3)
Change from baseline to year 10		
n	101	71
Mean (SD)	0.55 (1.5)	1.21 (1.6)
ANCOVA		
LSM (SE)	0.58 (0.154)	1.17 (0.185)
Difference in LSMs	−0.59	
p-value	0.0155	
Secondary assessments		
Disability progression,[a] n/m (%)	35/101 (34.7) $p < 0.01$	37/66 (56.1)
Patients with EDSS <6, n/m (%)	90/101 (89.1) $p < 0.05$	54/71 (76.1)
Time to first use of ambulatory assistive devices, years		
Mean (SD)	8.3 (2.3)	5.2 (3.1)
Median	8.3	4.9
Time to first documented EDSS ≥6.0, years		
Mean (SD)	7.7 (2.5)	5.9 (3.6)
Median	8.1	5.7
Time to first use of a wheelchair, years		
Mean (SD)	7.2 (2.5)	6.2 (2.5)
Median	7.8	6.7
Proportion of patients in need of a wheelchair		
Kaplan–Meier estimate	4.9	16.9
HR (95% CI)	0.24 (0.07–0.85) $p < 0.0276$	
Time to first classification as SPMS, years		
Mean (SD)	5.4 (4.7)	3.4 (6.0)
Median	6.5	3.8
Proportion of patients classified as having SPMS over 10 years[b]	*N*=102	*N*=67
Kaplan–Meier estimate	8.1	18.2
HR (95% CI)	0.34 (0.12–0.92) $p < 0.05$	

[a]Disability progression is defined as an increase in EDSS score of 1.5 (from baseline score 0), or 1 (from baseline score 1–5), or 0.5 (from baseline score >5).
[b]First classification as SPMS.
Data represented as mean (SD) unless specified otherwise.
ANCOVA: analysis of covariance; CI: confidence interval; EDSS: Expanded Disability Status Scale; HR: hazard ratio; LSM: least squares mean; *n*: number of patients in the treatment group; *m*: number of patients with non-missing values; SD: standard deviation; SE: standard error; SPMS: secondary progressive multiple sclerosis.

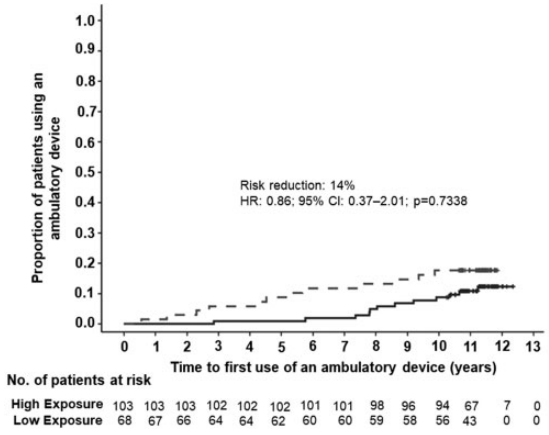

Figure 1. Kaplan–Meier plot of time to first use of an ambulatory assistive device by treatment group.
Fingolimod treatment: — High exposure - - - Low exposure + Censored.

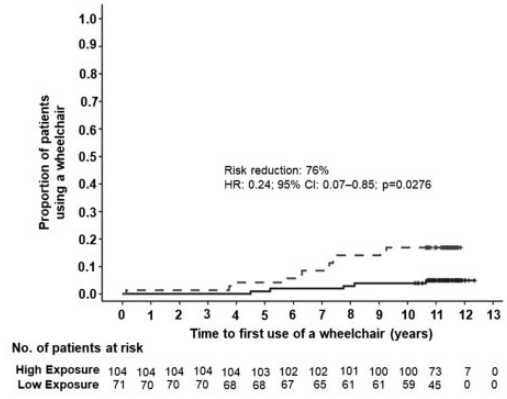

Figure 2. Kaplan–Meier plot of time to first use of a wheelchair by treatment group.
Fingolimod treatment: — High exposure - - - Low exposure + Censored.

Safety

AEs were only reported if they occurred during the one or two visits in this study and not retrospectively collected for the time since patients left the core study. No AEs considered serious, severe or drug-related were reported. Although effort was made to obtain information about patients who might have died since enrolling in the core study, no such cases were recorded. Overall, safety findings did not reveal any new safety issues associated with prolonged fingolimod treatment.

Discussion

This cross-sectional long-term follow-up study included 62% of the original Phase 2 study participants and provides information about long-term outcomes of fingolimod treatment. Approximately 60% of patients enrolled in ACROSS were exposed to fingolimod for ≥8 years (high exposure group). These patients had lower disability progression at the 10-year follow up, as measured by the change in EDSS score. This is further supported by the results of predictor analysis, where longer fingolimod treatment along with age at baseline showed significant correlation with change in EDSS over 10 years. Additionally, patients in the high exposure group had a longer time to first use of an ambulatory device or wheelchair and to conversion to SPMS compared with patients in the low exposure group. The cut-off defined for fingolimod treatment duration in this study is arbitrary and was based on the cut-off defined by Ebers et al. in the IFN β-1b long-term follow-up study.[11] An advantage of the chosen cut-off is that it resulted in roughly comparable group sizes for the high- and low-exposure groups. However, a potential drawback of this approach is that the groups have an imbalance in baseline co-variates possibly related to disease severity favoring the high exposure group. Therefore, a sensitivity analysis using treatment duration as a continuous parameter was performed. It corroborated the findings for the analysis using the arbitrary cut-off. However, the results should still be interpreted with caution.

In a study that evaluated IFN β-1a treatment in 122 of 172 initially enrolled patients with relapsing–remitting MS, the mean EDSS score increased from 2.2 at baseline to 5.1 at the 15-year follow-up.[15] Similarly, in a cross-sectional study with IFN β-1b, the EDSS score changed from 2.9 at baseline to a mean of 5.17 at the 16-year follow-up.[16] In another long-term follow-up study of 100 patients treated with glatiramer acetate (GA), the mean EDSS score increased from 2.5 at baseline to 3.1 after 15 years of follow-up.[17] In our study, patients in the high exposure group had a mean EDSS change from 2.16 at baseline to 2.72 at follow-up. A recent, large patient registry study of MS patients who were on IFN β-1a or GA treatment showed a median increase of one EDSS point from baseline to the date of censoring, and 17.8% of patients reached the milestone of an EDSS score ≥6 after ≥10 years of follow-up.[18] Our findings showed that a similar proportion (15.4%) of patients who interrupted fingolimod treatment reached the EDSS milestone of ≥6 whereas fewer patients (11.5%) in the ACROSS study who had high exposure to fingolimod reached EDSS ≥6. Similarly, mean time to

Table 4. MRI outcomes at year 10 by treatment group.

	Fingolimod treatment			
	High exposure ($N = 98$)	Low exposure ($N = 56$)	LSM difference	p value*
Total T2w lesion volume, mm^3				
n	98	54		
LSM (SE)	8703.8 (462.7)	11,310.1 (616.8)	−2606.3	<0.01
Number of new/enlarging T2w lesions				
n	96	53		
LSM (SE)	10.7 (1.8)	22.2 (2.4)	−11.45	<0.0001
T1w hypointense lesion volume, mm^3				
n	98	54		
LSM (SE)	3357.6 (252.3)	4216.2 (336.2)	−858.6	NS

*p values are derived from a Rank-ANCOVA test.
ANCOVA was performed with MRI parameter at year 10 as response variable, duration of MS disease, baseline T2 lesion volume, and baseline EDSS as continuous covariates, and treatment as fixed effect.
In the rank ANCOVA the outcome and all continuous covariates are replaced by their ranks.
ANCOVA: analysis of covariance; LSM: least squares mean; MRI: magnetic resonance imaging; NS: nonsignificant; SE: standard error; T1w: T1-weighted; T2w: T2-weighted.

the first use of walking assistance was longer in patients with high exposure to fingolimod compared to those who had low exposure. It is worth noting that the mean duration of MS since onset in patients who participated in the ACROSS study was almost 20 years at follow-up. It is also important to consider the baseline EDSS scores, because a higher baseline EDSS score might have led to the early use of ambulatory devices.

At follow-up, the number of new/enlarging T2w lesions and accumulation of T2 lesion volume were reduced in the high exposure group, comparable to the beneficial effects of fingolimod on MRI endpoints in the Phase 3 trials.[5,19] However, there was no correlation between the treatment duration and the MRI outcomes at 10 years. Differences in image acquisition and resolution and other technical changes over time might have to be taken into account.

Compared to core baseline, patients in the high exposure group were stable in MSFC z-score and improved in PASAT-3 score at follow-up whereas patients in the low-exposure group exhibited a worsening. However, no significant difference between the two treatment groups was observed for T25FWT or 9-HPT scores. A learning effect on the PASAT-3 test cannot be excluded because patients in the high exposure group enrolled in fingolimod extension studies had more PASAT tests in the 10-year period than those in the low exposure group.

When interpreting the results of the ACROSS study, it is important to note the patients in the high exposure group had a lower EDSS score, a shorter disease duration and lower T2w lesion volume at baseline compared with the low exposure group. Along the same line, one-third of patients in the low exposure group were switched to a high efficacy treatment after stopping fingolimod. Because these aspects may reflect different disease activity in the two groups, intrinsic evolution of the disease may have contributed to positive efficacy outcomes in the high exposure group. Also, the response to fingolimod treatment might be better in this group because subgroup analyses of Phase 3 studies have shown fingolimod had a slightly stronger effect on relapse rates in patients with a lower EDSS score and shorter disease duration.[20] The beneficial response in the high exposure group may therefore be attributable to four different factors: (a) an effect of fingolimod on the disease course independent of the baseline characteristics; (b) a stronger treatment response to fingolimod in patients with a shorter disease duration and lower EDSS score at treatment start; (c) a more benign disease course independent of the treatment; and (d) treatment satisfaction or dissatisfaction leading to longer or shorter exposure, as non-responders to fingolimod or patients with severe disease are likely to switch to other drugs. Given the lack of a matched control cohort, it is not possible to estimate the magnitude of the beneficial contribution of these factors. However, it is plausible that these four

factors may have all contributed to the outcomes at follow-up. It would certainly be worthwhile to compare the high exposure population with a propensity score-matched real-world population to distinguish the treatment effects from a potential selection bias. Other limitations for consideration are that varied DMTs were used among patients who had discontinued fingolimod, there were varying treatment durations in patients who had stopped fingolimod, and the ascertainment rate of 62% for the overall study (84.0% for the participating sites).

In conclusion, disability progression in this study cohort is low with over 80% of patients below an EDSS of 6, almost 20 years after onset of disease. This proportion is even further increased in patients with high fingolimod exposure. The effects seen for high fingolimod exposure are consistent with the efficacy reported previously in 5- and 7-year extension studies. The high persistence rate among patients willing to undergo another assessment 10 years or more after the start of the initial Phase 2 study indicates patients and prescribers perceive fingolimod to be an effective, safe, and well-tolerated treatment.

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Conflict of Interests

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Supplemental material

Supplemental material for this article is available online.

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