



# Long-Term Effect of Immediate Versus Delayed Fingolimod Treatment in Young Adult Patients with Relapsing–Remitting Multiple Sclerosis: Pooled Analysis from the FREEDOMS/FREEDOMS II Trials

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## ABSTRACT

**Introduction:** Fingolimod has demonstrated clinical and MRI benefits versus placebo/interferon  $\beta$ -1a in young adults with multiple sclerosis (MS). Here we report the long-term effects of fingolimod 0.5 mg on clinical and MRI outcomes in young adults with MS aged  $\leq 30$  years followed up for up to 8 years (96 months).

**Methods:** This post hoc analysis of pooled FREEDOMS/FREEDOMS II studies included patients who either received fingolimod 0.5 mg from randomization (immediate;  $N = 163$ ) or switched from placebo to fingolimod at month (M) 24 (delayed;  $N = 147$ ). The 6-month

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confirmed disability improvement [6m-CDI: based on Expanded Disability Status Scale (EDSS)], 6m-CDI-plus (6m-CDI+; EDSS, 9-Hole Peg Test, Timed 25-Foot Walk Test), 6-month confirmed disability progression (6m-CDP), time to EDSS score  $\geq 4$ , annualized relapse rates (ARRs), new/newly enlarging T2 (neT2) lesions, and annual rate of brain volume loss (BVL) were analyzed from baseline to M24, M48, and M96. Cox regression and negative binomial regression models were used to analyze measured outcomes.

**Results:** At baseline, more than two-thirds of young adult patients were treatment naïve, had more than two relapses in the previous 2 years, and EDSS score  $< 2$ . From M0 to M96, a significantly higher proportion of young adult patients in the immediate group (vs. delayed group) achieved 6m-CDI (58.2% vs. 30.5%,  $p = 0.0206$ ) and 6m-CDI+ (70.6% vs. 42.3%,  $p = 0.0149$ ); significantly fewer patients reached 6m-CDP (20.1% vs. 34.7%,  $p = 0.0058$ ) and EDSS  $\geq 4$  (24.1% vs. 34.1%,  $p = 0.0041$ ). Up to M96, young adults in the immediate versus delayed group had lower ARR (0.16 vs. 0.38,  $p < 0.0001$ ) and a higher proportion of patients were free of neT2 lesions at M48 (31.0% vs. 5.0%,  $p = 0.0011$ ).

**Conclusion:** In young adult patients with MS, immediate versus delayed fingolimod treatment was associated with improved disease outcomes and greater long-term benefits in both disease activity and disability progression.

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**Keywords:** Disability; Fingolimod; Multiple sclerosis; Relapse rates; Young adults

## INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disorder that typically manifests its symptoms in patients aged between 20 and 40 years, with a mean onset age of approximately 30 years [1, 2]. About 80–90% of people with MS experience a relapsing–remitting form of the disease (RRMS) that is often accompanied by an initially subtle subclinical progression [2, 3]. In patients with RRMS, the ability to recover from initial relapses declines with age [4], suggesting age at disease onset to be an important clinical factor for disability accumulation [5]. Evidence from population-based studies suggests that pediatric and young patients with MS take longer to reach disability milestones, but they tend to do so at a younger age than the adult MS population [6–8]. In post hoc analyses and retrospective studies, pediatric and young adult patients with relapsing MS reported higher relapse rates (two to three times higher) and brain lesion activity compared with their older adult counterparts [9–11]. This suggests that younger patients with MS experience a more inflammatory disease course than older patients with MS.

Early initiation of high-efficacy disease-modifying therapies (DMTs) in patients with MS is important to prevent irreversible damage that may already occur at disease onset and early in the disease course [12, 13]. Several studies have shown that early treatment with DMTs in patients with active MS provides better disease control by reducing relapse activity and disability accrual when compared to delayed therapy over the long term [14–18]. However, despite significant disease burden, use of DMTs in pediatric patients with MS is based mainly on small retrospective and observational studies. To date, there is only one randomized controlled study completed in the pediatric population. PARADIGMS (NCT01892722) evaluated

the safety and efficacy of oral fingolimod compared to interferon beta-1a (IFN  $\beta$ -1a) in children and adolescents [19]. Once-daily oral fingolimod 0.5 mg (Gilenya<sup>®</sup>, Novartis Pharma AG) is the first-in-class sphingosine-1-phosphate receptor modulator approved for the treatment of RRMS in adult patients.

On the basis of the results from PARADIGMS, where fingolimod demonstrated significant benefit over intramuscular IFN  $\beta$ -1a in pediatric patients with MS [19], the US Food and Drug Administration [20] and the European Medicines Agency [21] approved fingolimod for the treatment of children and adolescents with relapsing MS aged 10 to less than 18 years worldwide. In addition, fingolimod 0.5 mg versus placebo and IFN  $\beta$ -1a has demonstrated treatment benefits in young adults with RRMS on clinical and magnetic resonance imaging (MRI) measures [9]. In a post hoc analysis of data from three phase 3 fingolimod trials (FREEDOMS, FREEDOMS II, and TRANSFORMS), fingolimod 0.5 mg versus placebo and IFN  $\beta$ -1a significantly reduced annualized relapse rate (ARR) and new/newly enlarging T2 (neT2) lesions in young adult patients ( $\leq 20$  years and  $\leq 30$  years of age) compared with the overall adult population [9]. The odds of achieving no evidence of disease activity status over 2 years was found to be strongest in the youngest patients ( $\leq 20$  years of age) treated with fingolimod 0.5 mg versus both placebo and IFN  $\beta$ -1a [9]. Here we report the long-term effects of fingolimod 0.5 mg on clinical and MRI outcomes in young adult patients aged  $\leq 30$  years who were followed up for up to 8 years in the pooled FREEDOMS studies.

## METHODS

### Study Design and Patients

This post hoc analysis included young adult patients ( $\leq 30$  years) with RRMS from the pooled, placebo-controlled FREEDOMS (NCT00289978)/FREEDOMS II (NCT00355134) studies who were followed for up to 8 years. In the core phase, patients were randomized to fingolimod 1.25 mg or 0.5 mg or placebo

[16, 22, 23]. After 24 months, patients who had received fingolimod in the core phase continued to receive the same dose and those who had received placebo were re-randomized to fingolimod 1.25 mg or 0.5 mg. Patients who were re-randomized to 1.25 mg were subsequently switched to 0.5 mg.

For the purpose of this post hoc analysis, we compared patients randomized to and continuously treated with the approved dose of fingolimod 0.5 mg (immediate fingolimod) versus those initially randomized to placebo and then switched to fingolimod at month 24 (delayed fingolimod). Patients initially randomized to fingolimod 1.25 mg in the core study and later switched to fingolimod 0.5 mg were excluded from this analysis. Young adult patients from the immediate and delayed fingolimod groups were also compared with the overall analysis population, which included all patients from the pooled FREEDOMS and FREEDOMS II studies. Similar comparisons were made in the overall analysis population who were grouped under an overall immediate fingolimod group and overall delayed fingolimod group, respectively.

### Assessments

The key efficacy outcomes, including disability, relapses, and MRI outcomes, were analyzed from month (M) 0 to M24, M48, and M96. The time-to-event outcomes included 6-month confirmed disability improvement (6m-CDI), 6m-CDI-plus (6m-CDI+), 6-month confirmed disability progression (6m-CDP), and Expanded Disability Status Scale (EDSS) score  $\geq 4.0$ . 6m-CDI was defined as 6 months of confirmed EDSS score decrease by  $\geq 1.0$  from a baseline EDSS score of  $\leq 5.5$ , or by  $\geq 0.5$  from a baseline EDSS score of  $\geq 6.0$ . 6m-CDI+ was defined as 6m-CDI or 6 months of confirmed  $\geq 20\%$  improvement in 9-Hole Peg Test (9-HPT) or the Timed 25-Foot Walk Test (T25FWT). Disability progression, 6m-CDP, was defined as 6 months of confirmed EDSS worsening of  $\geq 1.5$  if baseline EDSS score was  $= 0$ , of  $\geq 1$  if baseline EDSS score was between 1 and 5, and of  $\geq 0.5$  if baseline EDSS score was  $> 5$ . The ARR was defined as the

number of confirmed relapses per year. Measures of efficacy on MRI included the cumulative number of neT2 lesions, the proportion of patients free of neT2 lesions, and the annualized rate of brain atrophy (ARBA), i.e., the percentage of brain volume loss (BVL) per year. Safety data from the pooled FREEDOMS/FREEDOMS II studies for young adult patients in the immediate and delayed fingolimod groups were analyzed on the basis of adverse events (AEs) and compared with the overall analysis population.

### Statistical Analysis

Time-to-event outcomes were analyzed using Kaplan–Meier estimates and Cox regression. The Cox regression models were adjusted for sex, age, baseline EDSS score, and number of relapses in the 2 years prior to the study. Patients with baseline EDSS score  $\leq 2.0$  were excluded for 6m-CDI and 6m-CDI+ (ceiling effect) analysis, and patients with baseline EDSS score  $\geq 4.0$  were excluded for the time to EDSS  $\geq 4.0$  analysis. ARR was analyzed using a negative binomial regression model with log (-time in study in years) as an offset variable and was adjusted for sex, age, baseline EDSS score, and number of relapses in the 2 years before the study. Cumulative numbers of neT2 lesions were analyzed using a negative binomial regression model adjusted for treatment, sex, age, and volume of T2 lesions at baseline. Freeness from neT2 lesions was analyzed using logistic regression models with treatment, sex, age, and baseline T2 lesion volume as the exploratory variables. If the total number of patients was less than five in any treatment group or all of the patients had the same response level in any treatment group, Fisher's exact test was performed instead of logistic regression. A linear regression model with treatment, sex, age, and normalized brain volume at baseline as explanatory variables was used to analyze ARBA, which was approximately normally distributed. Safety outcomes were summarized descriptively. Reported AEs were compared in the immediate ( $n = 783$ )

versus delayed ( $n = 773$ ) fingolimod group of the overall analysis population.

### Compliance with Ethics Guidelines

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for inclusion in the study. The FREEDOMS and FREEDOMS II studies were approved by central and local ethics committees and were conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice and the Declaration of Helsinki.

## RESULTS

Of the total 2355 patients pooled from the FREEDOMS/FREEDOMS II studies who underwent randomization, 1556 patients were randomized to

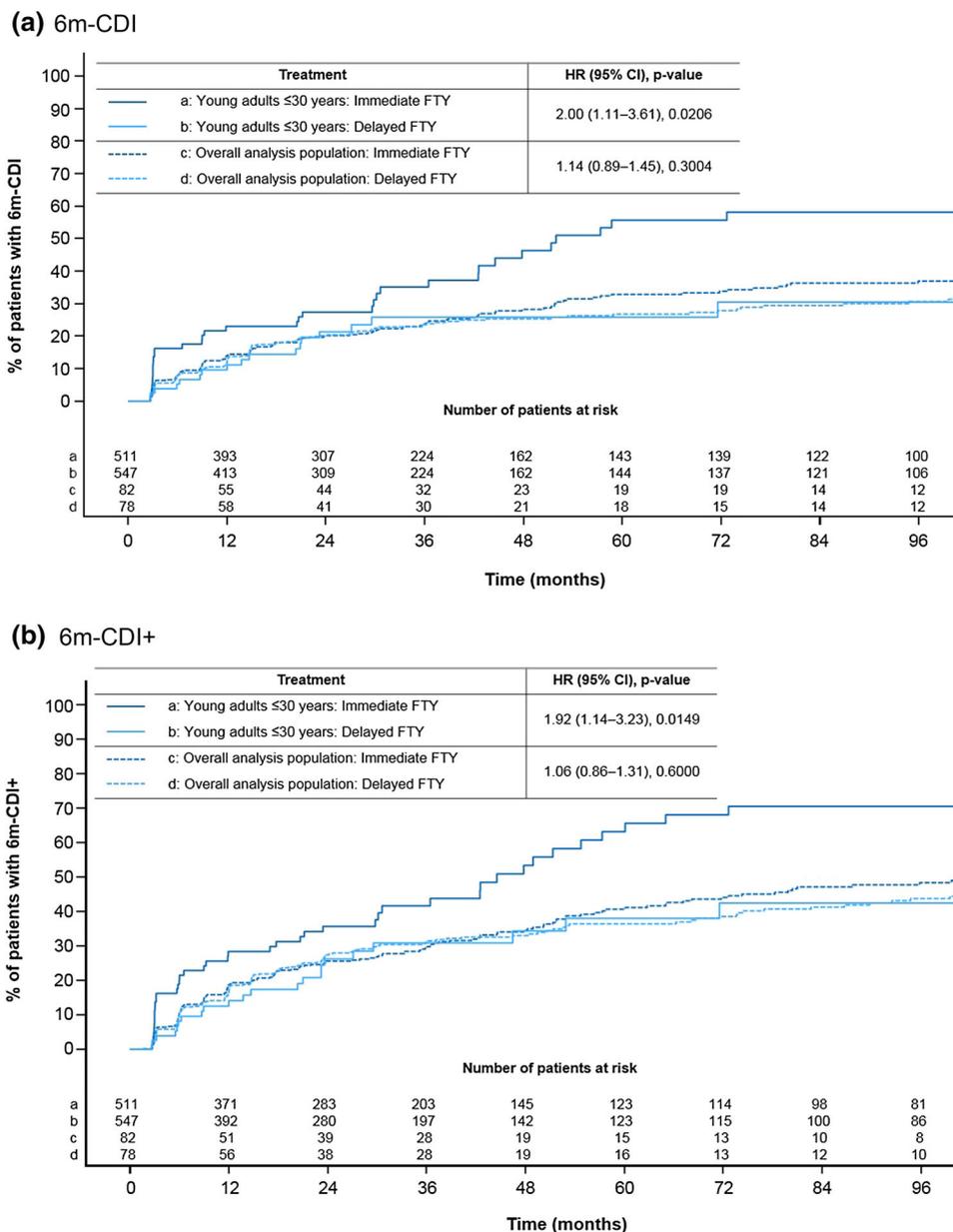
either fingolimod 0.5 mg or placebo (overall analysis population); 799 patients who were initially randomized to fingolimod 1.25 mg during the core study were excluded for this post hoc analysis. Approximately 20% (310/1556) of the overall analysis population were aged 30 years or less, of which 52.6% (163/310) were in the immediate fingolimod group and 47.4% (147/310) were in the delayed fingolimod group. The demographics and baseline disease characteristics of young adult patients aged  $\leq 30$  years and the overall analysis population are shown in Table 1. At baseline, two-thirds of the young adult patients were female, with an average age of 25 years. Young adult patients had a shorter disease duration, a lower EDSS score, and a higher number of gadolinium-enhancing (Gd+) T1 lesions than the overall analysis population. In the 2 years prior to the study, young patients had two or more relapses (at least one relapse in the previous year or at least two relapses in the previous 2 years was mandated by the clinical protocol). Baseline characteristics of the immediate fingolimod group were similar to those of the delayed fingolimod group.

**Table 1** Baseline characteristics of young adult patients and the overall analysis population from pooled FREEDOMS/FREEDOMS II studies

Characteristic	Young adult patients ( $N = 310$ )		Overall analysis population ( $N = 1556$ )	
	Immediate FTY ( $n = 163$ )	Delayed FTY ( $n = 147$ )	Immediate FTY ( $n = 783$ )	Delayed FTY ( $n = 773$ )
Age, years	25.8 $\pm$ 3.29	25.9 $\pm$ 3.11	38.4 $\pm$ 8.83	38.6 $\pm$ 8.63
Female, $n$ (%)	115 (70.6)	101 (68.7)	571 (72.9)	586 (75.8)
Duration of MS since first symptom, years	4.5 $\pm$ 3.49	4.3 $\pm$ 3.54	9.1 $\pm$ 7.37	9.3 $\pm$ 7.18
Number of relapses in the previous 2 years	2.4 $\pm$ 1.49	2.2 $\pm$ 1.32	2.2 $\pm$ 1.26	2.2 $\pm$ 1.33
EDSS score	2.0 $\pm$ 1.22	1.8 $\pm$ 1.09	2.3 $\pm$ 1.31	2.5 $\pm$ 1.30
Number of Gd+ T1 lesions	3.0 $\pm$ 8.62	2.4 $\pm$ 5.32	1.5 $\pm$ 4.70	1.2 $\pm$ 3.07
Volume of T2 lesions, mm <sup>3</sup>	6240.1 $\pm$ 8148.83	5330.8 $\pm$ 5992.22	5821.8 $\pm$ 7796.84	5860.8 $\pm$ 7424.44
Normalized brain volume, cm <sup>3</sup>	1569.7 $\pm$ 74.94	1580.1 $\pm$ 77.86	1521.5 $\pm$ 82.89	1518.7 $\pm$ 85.60

Data presented are mean  $\pm$  SD, unless otherwise specified

EDSS Expanded Disability Status Scale, FTY fingolimod, Gd+ gadolinium-enhancing, MS multiple sclerosis, SD standard deviation



**Fig. 1** Kaplan–Meier estimates for time to 6m-CDI (a) and 6m-CDI+ (b) in young adult patients and the overall analysis population from pooled FREEDOMS/FREEDOMS II studies. The Cox regression model was adjusted for sex, age, baseline EDSS and number of relapses in the 2 years prior to the study. Subjects with baseline

EDSS score < 2.0 were excluded for 6m-CDI. Subjects with baseline EDSS score ≤ 2.0 were excluded for 6m-CDI+ 6m-CDI 6-month confirmed disability improvement, 6m-CDI+ 6-month confirmed disability improvement-plus, CI confidence interval, EDSS Expanded Disability Status Scale, FTY fingolimod, HR hazard ratio

**Clinical Outcomes**

**Time to 6m-CDI and 6m-CDI+**

A greater proportion of young adult patients achieved 6m-CDI and 6m-CDI+ over

96 months in the immediate fingolimod group compared with the delayed fingolimod group (6m-CDI: 58.2% vs. 30.5%; 6m-CDI+: 70.6% vs. 42.3%) (Fig. 1a, b). The probability of achieving both 6m-CDI and 6m-CDI+ in the immediate

versus delayed fingolimod group was higher in young adult patients [6m-CDI: hazard ratio (HR) 2.00 (95% confidence interval (CI) 1.11–3.61),  $p = 0.0206$ ; and 6m-CDI+: 1.92 (1.14–3.23),  $p = 0.0149$ ] and in the overall analysis population [6m-CDI: 1.14 (0.89–1.45),  $p = 0.3004$ ; and 6m-CDI+: 1.06 (0.86–1.31),  $p = 0.6000$ ]. Moreover, the difference in the proportion of patients achieving 6m-CDI and 6m-CDI+ over 96 months between the immediate and delayed fingolimod groups was greater in young adult patients compared with the overall analysis population.

**Time to 6m-CDP**

In young adult patients, the risk of 6m-CDP was 54% lower in the immediate fingolimod group compared with the delayed fingolimod group. Over 96 months, the treatment effect of immediate fingolimod in reducing the risk of 6m-CDP versus delayed fingolimod was stronger in young adult patients [HR 0.46 (95% CI 0.27–0.80),  $p = 0.0058$ ] than in the overall

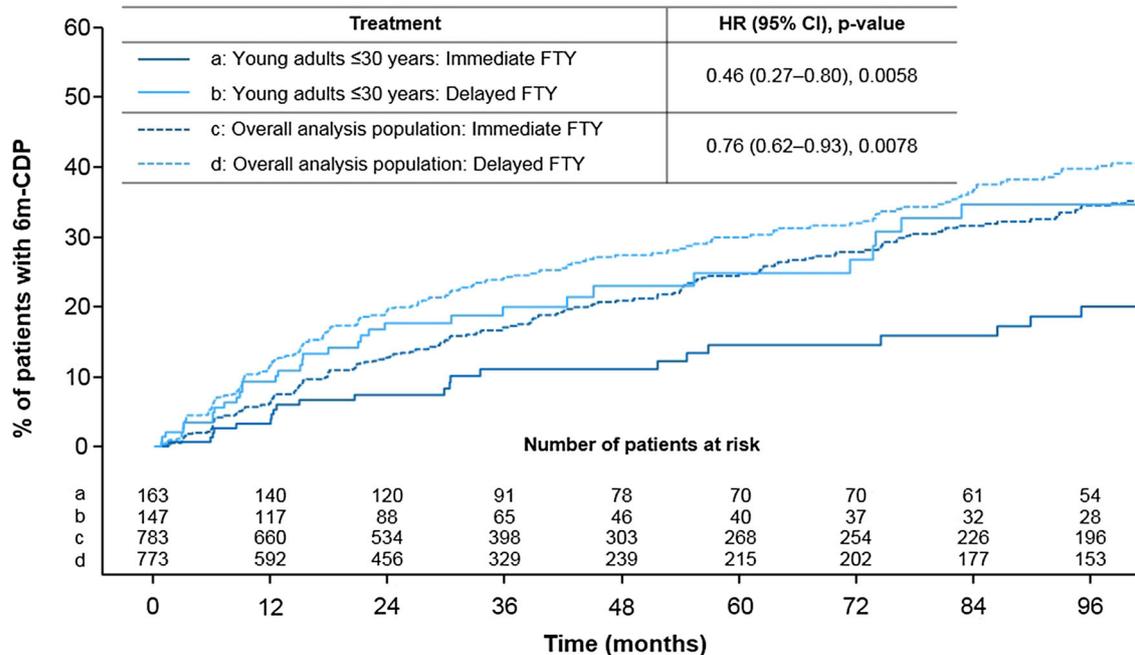
analysis population [0.76 (0.62–0.93),  $p = 0.0078$ ] (Fig. 2).

**Time to EDSS  $\geq 4.0$**

Compared with the delayed fingolimod group, the proportion of young adult patients in the immediate fingolimod group reaching EDSS  $\geq 4.0$  was significantly lower (Fig. 3). Immediate fingolimod compared with delayed fingolimod reduced the risk of reaching EDSS  $\geq 4$  over 96 months in all patients; however, the treatment effect of immediate fingolimod versus delayed fingolimod was stronger in the young adult patients [HR 0.48 (95% CI 0.29–0.80),  $p = 0.0044$ ] than in the overall analysis population [0.68 (0.55–0.83),  $p = 0.0001$ ].

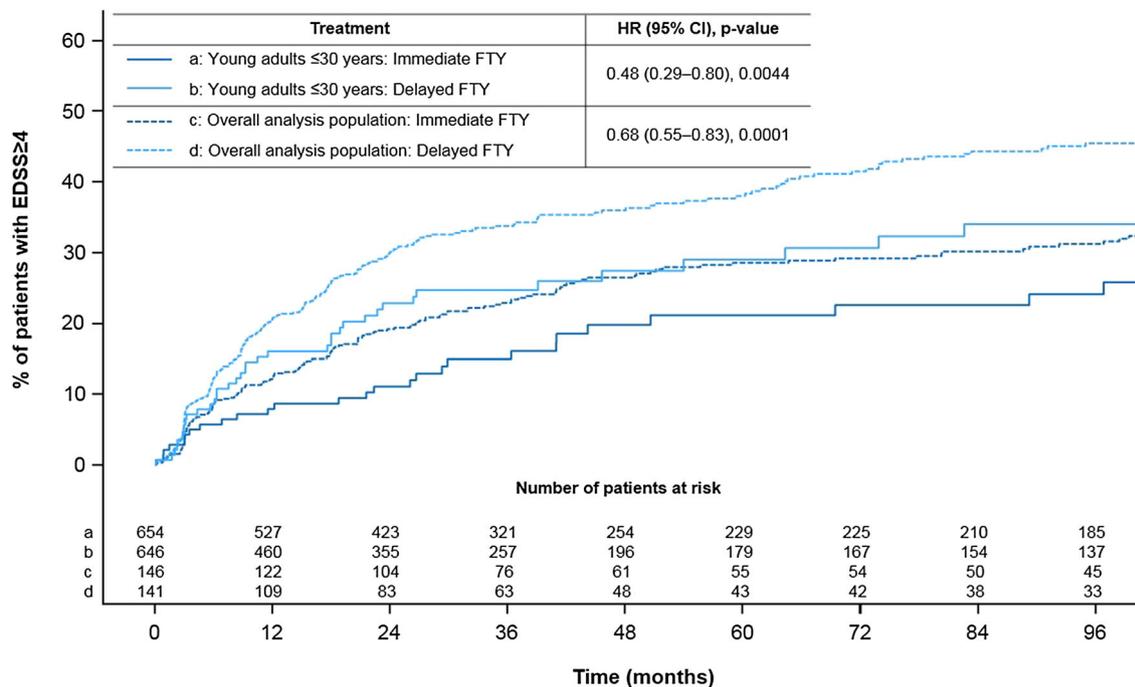
**ARRs**

The ARR from baseline to month 24 were significantly lower in fingolimod-treated patients compared with placebo-treated patients in young adults and in the overall analysis population, with relative reductions of 62%



**Fig. 2** Kaplan–Meier estimates for time to 6m-CDP in young adult patients and the overall analysis population from pooled FREEDOMS/FREEDOMS II studies. The Cox regression model was adjusted for sex, age, baseline

EDSS, and number of relapses in the 2 years prior to the study. 6m-CDP 6-month confirmed disability progression, CI confidence interval, EDSS Expanded Disability Status Scale, FTY fingolimod, HR hazard ratio



**Fig. 3** Time to EDSS  $\geq 4.0$  in young adult patients and the overall analysis population from pooled FREEDOMS/FREEDOMS II studies. The Cox regression model was adjusted for sex, age, baseline EDSS, and number of

relapses in the 2 years prior to the study. Subjects with baseline EDSS score  $\geq 4.0$  were excluded. CI confidence interval, EDSS Expanded Disability Status Scale, FTY fingolimod, HR hazard ratio

( $p < 0.0001$ ) and 52% ( $p < 0.0001$ ), respectively. Patients in the immediate fingolimod group had consistently lower ARRs than those in the delayed fingolimod group in both young adults and the overall analysis population. At M96, patients immediately and continuously treated with fingolimod in the young adult and overall analysis population had an ARR of 0.16 and 0.15, respectively. The difference in the percentage of reduction in ARR between the immediate and delayed fingolimod groups was higher in the young adult patients compared with the overall analysis population (Fig. 4).

**MRI Outcomes**

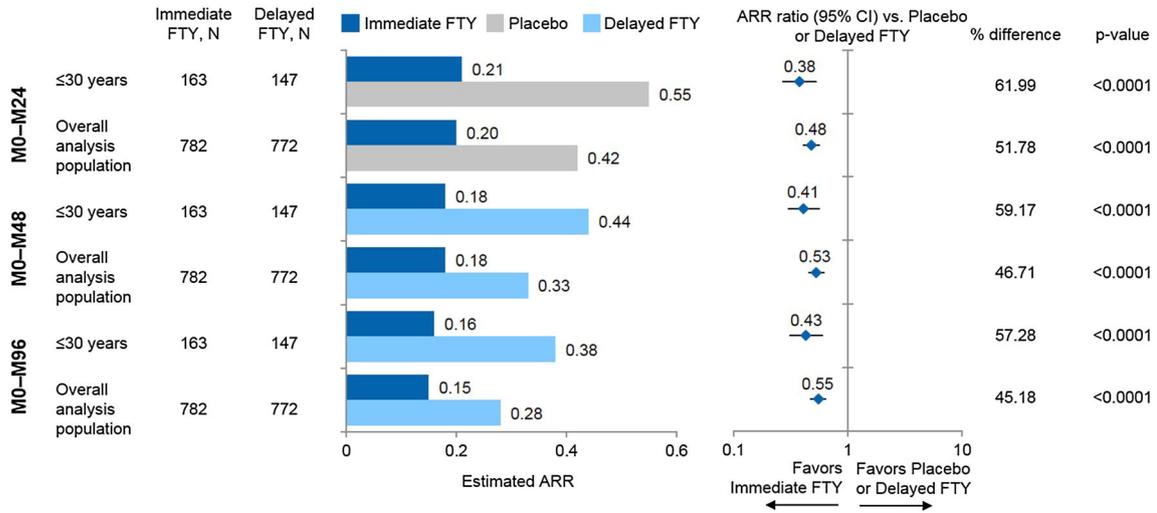
**Number of neT2 Lesions**

Young adult patients had a higher number of neT2 lesions compared with the overall analysis population at all time points. The numbers of neT2 lesions from baseline to M24 were significantly lower with fingolimod compared with placebo in the overall analysis population and

young adult patients with relative reductions of 74% ( $p < 0.0001$ ) and 77% ( $p < 0.0001$ ), respectively. At all time points, young adult patients in the immediate fingolimod group had significantly lower cumulative numbers of neT2 lesions compared with those in the delayed fingolimod group (Fig. 5).

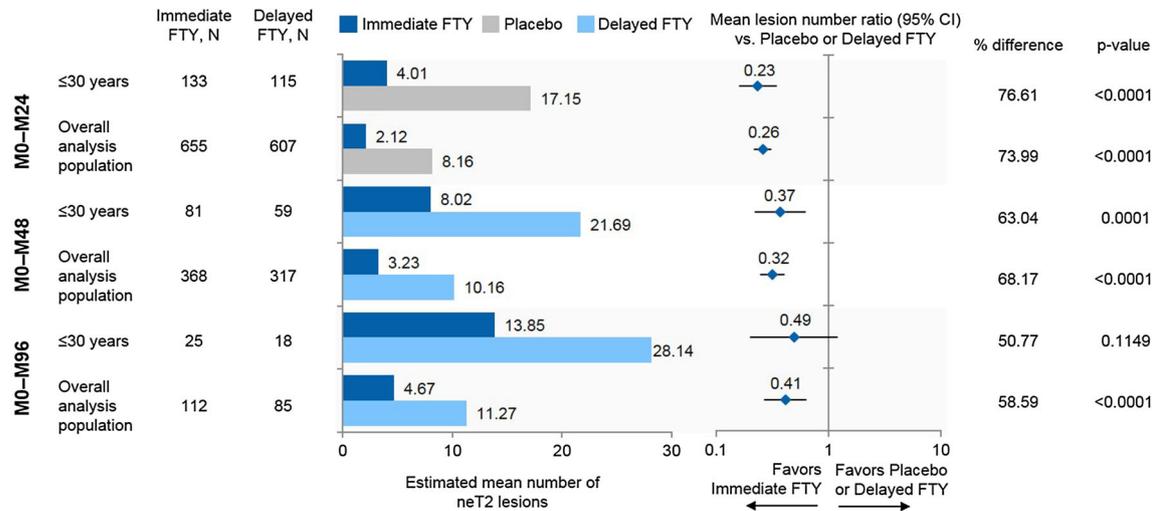
**Proportion of Patients Free of neT2 Lesions**

Patients treated immediately with fingolimod had a higher chance of remaining free of neT2 lesions compared to the patients in the delayed fingolimod group. The relative reduction in lesion formation was always stronger in young adults than in the overall analysis population (Fig. 6). Approximately 30% of young adult patients in the immediate fingolimod group were free of neT2 lesions over 96 months. In the overall analysis population, compared with the delayed group, significantly higher numbers of patients in the immediate fingolimod group were free of neT2 lesions from baseline to M48 and M96 ( $p < 0.0001$ , for both).



**Fig. 4** Estimated ARRs in young adult patients and the overall analysis population from pooled FREEDOMS/FREEDOMS II studies. The negative binomial regression model, with log (time in study in years) as an offset variable, was adjusted for sex, age, baseline EDSS, and number of relapses in the 2 years prior to the study. An

ARR ratio of < 1 between fingolimod and placebo signifies a treatment benefit of fingolimod. ARR annualized relapse rate, CI confidence interval, EDSS Expanded Disability Status Scale, FTY fingolimod, M month, N number of subjects included in the analysis



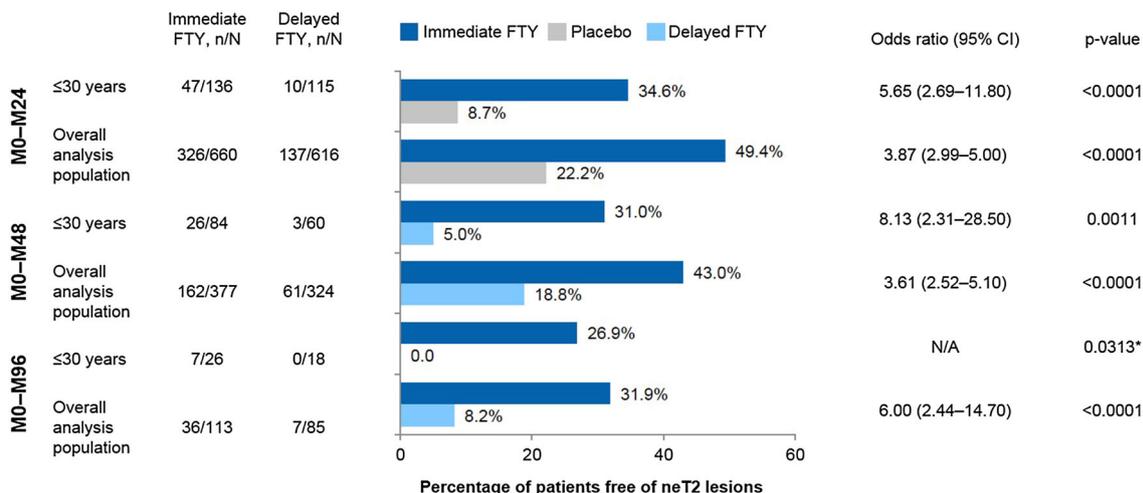
**Fig. 5** Estimated number of neT2 lesions in young adult patients and the overall analysis population from pooled FREEDOMS/FREEDOMS II studies. The negative binomial regression model was adjusted for treatment, sex, age, and volume of T2 lesions at baseline. An neT2 lesion rate

ratio of < 1 between fingolimod and placebo signifies a treatment benefit of fingolimod. CI confidence interval, FTY fingolimod, M month, N number of subjects included in the analysis, neT2 new/newly enlarging T2 lesions

**ARBA**

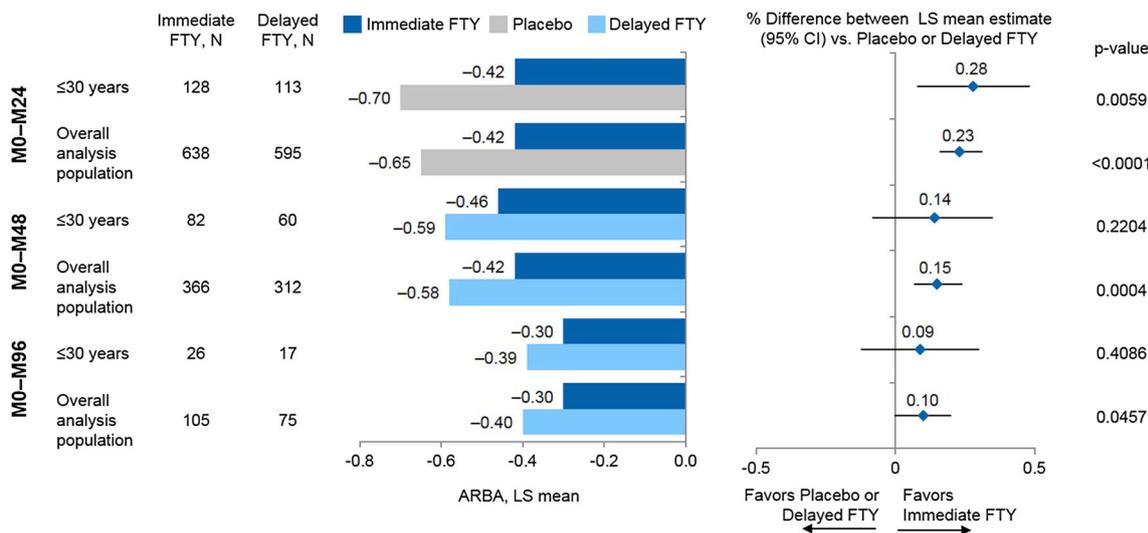
Brain volume loss, as measured by ARBA, was similar in the young adults and the overall analysis population. Fingolimod reduced brain

volume loss versus placebo from baseline to M24 (core phase of the trials) in the overall analysis population [least square (LS) mean difference 0.23 (95% CI 0.16–0.31), *p* < 0.0001]



**Fig. 6** Proportions of patients free of neT2 lesions in the pooled FREEDOMS/FREEDOMS II studies. \**p* value is from Fisher’s exact test. The logistic regression model was adjusted for treatment, sex, age, and baseline T2 lesion volume. If the total number of patients was less than five in any treatment group or all of the patients had the same response level in any treatment group, Fisher’s exact test

was performed instead of logistic regression. CI confidence interval, FTY fingolimod, M month, N total number of patients in any treatment group category included in the analysis, n number of patients without neT2 lesions in the same category, N/A not applicable, neT2 new/newly enlarging T2 lesions



**Fig. 7** Annualized rate of brain atrophy in young adult patients and the overall analysis population from pooled FREEDOMS/FREEDOMS II studies. The linear regression model was adjusted for treatment, sex, age, and normalized brain volume at baseline. ARBA annualized and in young adults [0.28 (0.08–0.48), *p* = 0.0059]. The treatment difference in ARBA between the immediate and delayed

rate of brain atrophy (percentage brain volume change standardized to 1 year), CI confidence interval, FTY fingolimod, LS least squares, M month, N total number of patients in any treatment group category included in the analysis

fingolimod groups lessened over time, but was still notable after treatment over 96 months (Fig. 7).

## Safety

The AE profile of fingolimod in young adult patients and the overall analysis population is shown in Table 2. In the overall analysis population, the most common AEs in the immediate fingolimod group were nasopharyngitis (34.0%), headache (31.3%), upper respiratory tract infection (27.3%), and diarrhea (17.6%). The frequency of AEs reported in the young adults was similar to those reported in the overall analysis population. In young adult patients, the most common AEs (with an incidence of at least 15% in the immediate fingolimod group) included nasopharyngitis (33.7%), headache (33.1%), upper respiratory tract infection (30.7%), diarrhea (18.4%), back pain (16.6%), cough (16.6%), urinary tract infection (15.3%), influenza (15.3%), bronchitis (15.3%), and increased levels of alanine aminotransferase (15.3%). Among other AEs which were reported in less 10% of patients, epilepsy was reported in three (1.8%) patients in the young adults group compared with seven (0.9%) patients in the overall analysis population. One case (0.6%) of macular edema was reported with fingolimod in the young adult group. This was similar to the AEs reported in the immediate fingolimod group in the overall analysis population. No new safety findings were observed in the young adult patients over the long term, with the overall frequency of AEs being similar across groups.

## DISCUSSION

This post hoc analysis of data from the pooled FREEDOMS/FREEDOMS II studies investigated the long-term efficacy and safety of fingolimod 0.5 mg over 8 years in young adult patients in comparison to the overall analysis population. At baseline, young adult patients were less disabled and had a higher normalized brain volume, but had more acute MRI lesions, than the overall analysis population. Relapse activity was similar in young adult patients and the overall analysis population, likely due to the inclusion criteria of the core trials, which mandated a minimum of one relapse in the previous year or

two relapses in the previous 2 years. We compared patients who were randomized to and then continuously treated with fingolimod 0.5 mg with those who were randomized to placebo and then switched to fingolimod after 2 years. Baseline demographics and clinical characteristics were similar between these groups. Young adult patients had higher on-study relapse rates and higher lesion activity compared with the overall analysis population, and the percentage of brain volume loss in the first 24 months was highest in young placebo-treated adult patients. The early appearance of brain volume loss is in line with previous observations [24] and is associated with preexisting T2 lesions and acute Gd+ MRI lesions in younger patients with MS [25]. Brain volume has previously been identified as an important predictor of long-term disease outcomes [25, 26]. Patients with a reduced normalized brain volume were significantly more likely to worsen earlier than patients with a high brain volume [26].

In our study, immediate treatment with fingolimod compared with delayed treatment significantly improved long-term disability outcomes in young adult patients. Young adult patients in the immediate fingolimod group had a significantly higher probability to improve in their disability, based on EDSS alone (6m-CDI) or based on EDSS, 9-HPT, and 25TWT combined (6m-CDI+). Furthermore, the risk of 6m-CDP was significantly reduced with immediate fingolimod treatment versus delayed treatment. Young adult patients in the immediate group experienced fewer relapses and fewer lesions than those in the delayed group. Young adult patients immediately and continuously treated with fingolimod had an ARR of only 0.15 over 8 years. Our results are in line with previous observations where the benefits of fingolimod treatment on relapse and MRI outcomes are more pronounced in young adult patients compared to the overall population [9].

Typically, patients with pediatric-onset MS experience much higher relapse rates and MRI lesion activity than their adult counterparts [11]. In our study, young adult patients had higher disease activity in terms of relapse and lesion formation compared with the overall analysis population. Evidence suggests that a

**Table 2** Most common AEs (> 10% incidence in the immediate fingolimod group) in young adult patients and the overall analysis population up to M96

AEs, <i>n</i> (%)	Young adults ( $\leq 30$ years)		Overall analysis population	
	Immediate FTY <i>N</i> = 163	Delayed FTY <i>N</i> = 147	Immediate FTY <i>N</i> = 783	Delayed FTY <i>N</i> = 773
Subjects with any AE	161 (98.8)	136 (92.5)	770 (98.3)	731 (94.6)
Infections and infestations				
Nasopharyngitis	55 (33.7)	44 (29.9)	266 (34.0)	199 (25.7)
Upper respiratory tract infection	50 (30.7)	33 (22.4)	214 (27.3)	159 (20.6)
Urinary tract infection	25 (15.3)	14 (9.5)	132 (16.9)	102 (13.2)
Influenza	25 (15.3)	8 (5.4)	129 (16.5)	65 (8.4)
Sinusitis	17 (10.4)	6 (4.1)	121 (15.5)	64 (8.3)
Bronchitis	25 (15.3)	7 (4.8)	119 (15.2)	34 (4.4)
Pharyngitis	18 (11.0)	7 (4.8)	61 (7.8)	32 (4.1)
Nervous system disorders				
Headache	54 (33.1)	28 (19.0)	245 (31.3)	174 (22.5)
Dizziness	12 (7.4)	10 (6.8)	89 (11.4)	65 (8.4)
Gastrointestinal disorders				
Diarrhea	30 (18.4)	12 (8.2)	138 (17.6)	74 (9.6)
Nausea	22 (13.5)	18 (12.2)	127 (16.2)	90 (11.6)
General disorders and administration site conditions				
Fatigue	24 (14.7)	16 (10.9)	106 (13.5)	74 (9.6)
Musculoskeletal and connective tissue disorders				
Back pain	27 (16.6)	8 (5.4)	131 (16.7)	69 (8.9)
Arthralgia	17 (10.4)	6 (4.1)	108 (13.8)	72 (9.3)
Pain in extremity	10 (6.1)	8 (5.4)	105 (13.4)	57 (7.4)
Respiratory, thoracic, and mediastinal disorders				
Cough	27 (16.6)	14 (9.5)	137 (17.5)	87 (11.3)
Dyspnea	15 (9.2)	4 (2.7)	84 (10.7)	53 (6.9)
Oropharyngeal pain	23 (14.1)	15 (10.2)	78 (10.0)	62 (8.0)
Investigations				
ALT increase	25 (15.3)	6 (4.1)	88 (11.2)	22 (2.8)

*AEs* adverse events, *ALT* alanine aminotransferase, *FTY* fingolimod, *M* month, *N* number of patients in the analysis set (used as a denominator in percentages), *n* number of patients with at least one qualifying event

high relapse rate in the first 2 years of the disease is associated with an increased risk of permanent disability later in the disease [27]. Patients with pediatric-onset MS take approximately 10 years longer than patients with adult-onset MS to reach a phase of secondary progression and irreversible disability [28], although they do so at a chronological age approximately 10 years younger than those with adult-onset disease [8, 29]. Although single lesions may have no clinical translation, there is ample evidence that the cumulative MRI burden as measured by persistent lesions or by a small normalized brain volume is predictive of long-term outcomes [3, 24].

Active mechanisms such as the greater adaptive-compensatory plasticity of brains and efficient repair mechanisms in young adult patients may explain the better recovery compared to older adult patients, even with more inflammation and higher disease burden [30]. Therefore, initiating high-efficacy DMTs early in the disease course in young adult patients when the brain displays greatest plasticity may improve disease control and long-term outcomes [31]. Evidence suggests that treatment with high-efficacy DMTs such as fingolimod, natalizumab, or alemtuzumab is more potent in suppressing relapse activity when initiated early compared with a delay after the diagnosis of MS [17]. Treatment delay at an early stage of the disease can significantly decrease the cumulative efficacy of any DMT that cannot be regained even with aggressive treatments at a later stage [32]. In a post hoc subgroup analysis of TRANSFORMS and FREEDOMS data, patients treated early with fingolimod 0.5 mg showed better control of the disease when compared to treatment initiation with IFN  $\beta$ -1a or placebo during the core phase [33]. Similarly, in our analysis, young adult patients who were continuously treated with fingolimod during the core and extension phases showed better treatment effect than those who were re-randomized to fingolimod after 2 years on placebo. The treatment benefits of fingolimod on the clinical and MRI measures of disease activity observed during the short term were sustained in the long term when initiated early in the disease course in young adult patients.

The long-term benefits of fingolimod in adult patients with RRMS have been demonstrated in clinical trials [16, 34–36]. Data from pivotal phase 3 fingolimod studies suggest that fingolimod 0.5 mg was effective in reducing relapse rates by approximately 50% compared with either placebo at the end of year 2 [22, 23] or IFN  $\beta$ -1a at year 1 [37]. In addition, data from phase 3 extension studies have demonstrated that improvements in overall ARR after switching from IFN  $\beta$ -1a or placebo to fingolimod were sustained for up to 4 years (FREEDOMS) [16] and 4.5 years (TRANSFORMS) [36]. The long-term clinical benefits of fingolimod in patients with RRMS were associated with improved MRI outcomes and lower rates of brain volume loss [16, 36]. Our analyses extend previous observations where patients continuously treated with fingolimod showed better long-term outcomes across disability and clinical measures of disease activity, supporting the long-term treatment benefits of fingolimod in young adult patients with MS.

The safety profile of fingolimod 0.5 mg reported for young adult patients in the immediate fingolimod group was consistent with that observed in the overall analysis population. The most common AEs reported for young adult patients in the immediate fingolimod group included nasopharyngitis, headache, diarrhea, back pain, influenza, and increased levels of alanine aminotransferase, which were higher compared with the delayed fingolimod group. In addition, the proportions of patients with melanocytic nevus and skin papilloma were higher in the immediate versus delayed fingolimod group. However, these rates were similar to the overall analysis population. The incidence of infections was more frequent in the immediate fingolimod group compared with the overall analysis population. Incidence of rare AEs such as epilepsy and macular edema was low in the young adult population and was comparable to the overall analysis population. There were no cases of opportunistic infections reported. Our results are in line with previous observations in young adult patients as reported by Gartner et al. [9].

Fingolimod is the first and only DMT to be approved for pediatric MS patients. The

approval was supported by the PARADIGMS study, which showed a significant reduction of ARR, progression of disability, and MRI measures of disease activity in patients treated with fingolimod compared with IFN  $\beta$ -1a [19]. Despite the limitations inherent in long-term follow-up studies, the findings our post hoc analysis suggest that fingolimod can provide greater treatment benefits in patients of a younger age group compared with older patients with RRMS. The higher capacity of recovery together with highly active treatment results in better outcomes in the young adult population. Overall, within the MS continuum, starting from pediatric-onset MS, high inflammatory disease activity can be effectively treated with fingolimod.

## CONCLUSIONS

The study findings provide insights into the long-term efficacy and safety of fingolimod treatment in young adult patients with MS. Considering that accumulation of long-term disability is associated with higher disease activity early in the course of MS, early initiation with high-efficacy DMTs could lead to more favorable outcomes in patients with MS. In this post hoc analysis, young adult patients had higher disease activity in terms of ARR and lesion formation compared with the overall analysis population and two-thirds of the young adult patients were naïve to treatment. The treatment effect of fingolimod in terms of improvement in disability outcomes, relapse frequency, and MRI measures was evident across the treatment groups with young adult patients showing greater benefits. Moreover, BVL outcomes support the fact that BVL occurs similarly even in early stages as in the later stages of the disease. Patients in the immediate fingolimod group showed improved long-term clinical and MRI outcomes compared with the delayed fingolimod group, emphasizing the importance of early treatment. In the absence of any new safety issues, this data supports the long-term benefits of fingolimod treatment when initiated early in young adult patients with MS.

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**Compliance with Ethics Guidelines.** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for inclusion in the study. The FREEDOMS and FREEDOMS II studies were approved by central and local ethics committees and were conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice and the Declaration of Helsinki.

**Data Availability.** The datasets generated and/or analyzed during the current study are not publicly available because of patient confidentiality and compliance reasons, but are available from the corresponding author on reasonable request.

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## REFERENCES

- Kavaliunas A, Manouchehrinia A, Stawiarz L, et al. Importance of early treatment initiation in the clinical course of multiple sclerosis. *Mult Scler.* 2017;23(9):1233–40.
- Confavreux C, Vukusic S. Accumulation of irreversible disability in multiple sclerosis—lessons from natural history studies and therapeutic trials. *J R Coll Physicians Edinb.* 2004;34:268–73.
- Giovannoni G, Butzkueven H, Dhib-Jalbut S, et al. Brain health: time matters in multiple sclerosis. *Mult Scler Relat Disord.* 2016;9(Suppl 1):S5–48.
- Cosburn M, Ingram G, Hirst C, Ben-Shlomo Y, Pickersgill TP, Robertson NP. Age at onset as a determinant of presenting phenotype and initial relapse recovery in multiple sclerosis. *Mult Scler.* 2012;18(1):45–54.
- Confavreux C, Vukusic S. Age at disability milestones in multiple sclerosis. *Brain J Neurol.* 2006;129(Pt 3):595–605.
- Trojano M, Paolicelli D, Bellacosa A, Cataldo S. The transition from relapsing-remitting MS to irreversible disability: clinical evaluation. *Neurol Sci.* 2003;24(Suppl 5):S268–70.
- Renoux C. Natural history of multiple sclerosis: long-term prognostic factors. *Neurol Clin.* 2011;29(2):293–308.
- Harding KE, Liang K, Cosburn MD, et al. Long-term outcome of paediatric-onset multiple sclerosis: a population-based study. *J Neurol Neurosurg Psychiatry.* 2013;84(2):141–7.
- Gartner J, Chitnis T, Ghezzi A, et al. Relapse rate and MRI activity in young adult patients with multiple sclerosis: a post hoc analysis of phase 3 fingolimod trials. *Mult Scler J Exp Transl Clin.* 2018;4(2):2055217318778610.
- Benson LA, Healy BC, Gorman MP, et al. Elevated relapse rates in pediatric compared to adult MS persist for at least 6 years. *Mult Scler Relat Disord.* 2014;3(2):186–93.
- Gorman MP, Healy BC, Polgar-Turcsanyi M, Chitnis T. Increased relapse rate in pediatric-onset compared with adult-onset multiple sclerosis. *Arch Neurol.* 2009;66(1):54–9.
- Fernandez O. Is there a change of paradigm towards more effective treatment early in the course of apparent high-risk MS? *Mult Scler Relat Disord.* 2017;17:75–83.
- Pfeifenbring S, Bunyan RF, Metz I, et al. Extensive acute axonal damage in pediatric multiple sclerosis lesions. *Ann Neurol.* 2015;77(4):655–67.
- Comi G, Martinelli V, Rodegher M, et al. Effects of early treatment with glatiramer acetate in patients with clinically isolated syndrome. *Mult Scler.* 2013;19(8):1074–83.
- Kappos L, Freedman MS, Polman CH, et al. Long-term effect of early treatment with interferon beta-1b after a first clinical event suggestive of multiple sclerosis: 5-year active treatment extension of the phase 3 BENEFIT trial. *Lancet Neurol.* 2009;8(11):987–97.
- Kappos L, O'Connor P, Radue EW, et al. Long-term effects of fingolimod in multiple sclerosis: the randomized FREEDOMS extension trial. *Neurology.* 2015;84(15):1582–91.

17. Merkel B, Butzkueven H, Traboulsee AL, Havrdova E, Kalincik T. Timing of high-efficacy therapy in relapsing-remitting multiple sclerosis: a systematic review. *Autoimmun Rev*. 2017;16(6):658–65.
18. Miller AE, Wolinsky JS, Kappos L, et al. Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2014;13(10):977–86.
19. Chitnis T, Arnold DL, Banwell B, et al. Trial of fingolimod versus interferon beta-1a in pediatric multiple sclerosis. *N Engl J Med*. 2018;379(11):1017–27.
20. USFDA. <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm607501.htm>. Accessed 19 Feb 2019.
21. EMA. [https://www.ema.europa.eu/documents/overview/gilenya-epar-medicine-overview\\_en.pdf](https://www.ema.europa.eu/documents/overview/gilenya-epar-medicine-overview_en.pdf). Accessed 19 Feb 2019.
22. Calabresi PA, Radue EW, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2014;13(6):545–56.
23. Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med*. 2010;362(5):387–401.
24. De Stefano N, Airas L, Grigoriadis N, et al. Clinical relevance of brain volume measures in multiple sclerosis. *CNS Drugs*. 2014;28(2):147–56.
25. Radue EW, Barkhof F, Kappos L, et al. Correlation between brain volume loss and clinical and MRI outcomes in multiple sclerosis. *Neurology*. 2015;84(8):784–93.
26. Sormani MP, Arnold DL, De Stefano N. Treatment effect on brain atrophy correlates with treatment effect on disability in multiple sclerosis. *Ann Neurol*. 2014;75(1):43–9.
27. Bigi S, Banwell B. Pediatric multiple sclerosis. *J Child Neurol*. 2012;27(11):1378–83.
28. Boiko A, Vorobeychik G, Paty D, Devonshire V, Sadovnick D. Early onset multiple sclerosis: a longitudinal study. *Neurology*. 2002;59(7):1006–10.
29. Renoux C, Vukusic S, Mikaeloff Y, et al. Natural history of multiple sclerosis with childhood onset. *N Engl J Med*. 2007;356(25):2603–13.
30. Giorgio A, Zhang J, Stromillo ML, et al. Pronounced structural and functional damage in early adult pediatric-onset multiple sclerosis with no or minimal clinical disability. *Front Neurol*. 2017;8:608.
31. Noyes K, Weinstock-Guttman B. Impact of diagnosis and early treatment on the course of multiple sclerosis. *Am J Manag Care*. 2013;19(17 Suppl):s321–31.
32. Weideman AM, Tapia-Maltos MA, Johnson K, Greenwood M, Bielekova B. Meta-analysis of the age-dependent efficacy of multiple sclerosis treatments. *Front Neurol*. 2017;8:577.
33. Agius M, Meng X, Chin P, Grinspan A, Hashmonay R. Fingolimod therapy in early multiple sclerosis: an efficacy analysis of the TRANSFORMS and FREEDOMS studies by time since first symptom. *CNS Neurosci Ther*. 2014;20(5):446–51.
34. Khatri B, Barkhof F, Comi G, et al. Comparison of fingolimod with interferon beta-1a in relapsing-remitting multiple sclerosis: a randomised extension of the TRANSFORMS study. *Lancet Neurol*. 2011;10(6):520–9.
35. Meng X, Chin PS, Hashmonay R, Zahur Islam M, Cutter G. Effect of switching from intramuscular interferon beta-1a to oral fingolimod on time to relapse in patients with relapsing-remitting multiple sclerosis enrolled in a 1-year extension of TRANSFORMS. *Contemp Clin Trials*. 2015;41:69–74.
36. Cohen JA, Khatri B, Barkhof F, et al. Long-term (up to 4.5 years) treatment with fingolimod in multiple sclerosis: results from the extension of the randomised TRANSFORMS study. *J Neurol Neurosurg Psychiatry*. 2016;87(5):468–75.
37. Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med*. 2010;362(5):402–15.