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Early initiation of fingolimod reduces the rate of severe relapses over the long term: Post hoc analysis from the FREEDOMS, FREEDOMS II, and TRANSFORMS studies

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ABSTRACT

Background: Relapse frequency is often correlated with the prognosis of multiple sclerosis (MS). In patients with relapsing-remitting MS (RRMS), relapses vary in severity and may affect activities of daily living, require steroid intervention, or hospitalization. Incomplete recovery from relapses results in increasing disability. In pivotal phase III studies of fingolimod (FREEDOMS, FREEDOMS II, and TRANSFORMS), the frequency of overall and severe relapses was significantly reduced in patients with RRMS treated with fingolimod compared with placebo or intramuscular interferon β-1a (IFN β-1a). The objective of this study was to report the effect of early initiation of fingolimod on relapse severity in patients with RRMS.

Methods: This is a post hoc descriptive analysis of data from the pooled placebo-controlled FREEDOMS/FREEDOMS II studies and from the active-comparator TRANSFORMS study. Patients were analyzed under 2 groups: patients initially randomized to receive fingolimod 0.5 mg during the core phase and continued fingolimod 0.5 mg in the extension phase (immediate fingolimod group), and patients initially randomized to placebo or IFN β-1a during the core phase and switched to fingolimod during the extension phase (delayed fingolimod group). Annualized relapse rate (ARR) was estimated for severe relapses (defined as Expanded Disability Status Scale increase of >1 point, or >2-point change in 1 or 2 Functional Systems, respectively, or >1-point change in >4 Functional Systems). ARR was also estimated for relapses that affected activities of daily living, required steroid use, or hospitalization.

Results: In the pooled FREEDOMS/FREEDOMS II extensions, the immediate fingolimod group showed sustained reductions in the proportion (core: 15.8% and extension: 9.3%) and in ARR over 4 years (0.032 and 0.015) for severe relapses, in relapses requiring steroids (0.149 and 0.123), hospitalization (0.049 and 0.039) and relapses affecting activities of daily living (0.155 and 0.112). In the TRANSFORMS extension, similar reductions were observed in the immedaite group for the proportion of severe relapses (core: 11.8% and extension: 9.8%). ARR remained low over 2 years for severe relapses (0.024 and 0.018), relapses affecting activities of daily living (0.112 and 0.109), relapses requiring steroids (0.156 and 0.161) and hospitalization (0.027 and 0.033). Results in the FREEDOMS/FREEDOMS II and TRANSFORMS extensions for the delayed group were similar. In the TRANSFORMS extension, the proportion of severe relapses were 18.0% (core) and 11.1% (extension); there were significant reductions in ARR for severe relapses (core: 0.079 and extension: 0.029), relapses requiring steroids (0.366 and 0.232), hospitalization (0.092 and 0.055), and relapses affecting activities of daily living (0.285 and 0.144) (all $p < 0.0001$). Complete recovery was reported for the majority of relapses during the core and extension phases in both the immediate and delayed fingolimod groups (Pooled FREEDOMS/FREEDOMS II: immediate group 59.7%–65.5% and delayed group 64.9%–67.7%; TRANSFORMS: 72.1%–80.0% and

Abbreviations: ARR, annualized relapse rate; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; FS, Functional Systems; IFN β-1a, interferon β-1a; IM, intramuscular; MRI, magnetic resonance imaging; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis

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65.4%–70.8%).
Conclusions: In patients with RRMS, the frequency of severe relapses and relapse severity remained low in the immedaite fingolimod group over a period of 4 years. Reductions in the proportion of severe relapses post switch from IFN β-1a or placebo to fingolimod underscore the clinical benefit and the relevance of an early initiation of fingolimod.

1. Introduction

A majority of patients diagnosed with multiple sclerosis (MS) initially follow a relapsing-remitting disease course characterized by episodes of neurological impairment followed by periods of partial or complete recovery (remissions) (Goodin et al., 2016; Lublin et al., 2014). Relapses or exacerbation are defined as neurologic symptoms lasting at least 24 h in the absence of a systemic illness and preceded by at least 30 days of neurologic stability (Kappos et al., 2006; Group 1993). In patients with relapsing MS, incomplete recovery from an acute exacerbation may result in increased impairment/disability over time (Lublin et al., 2003). Incomplete remissions are linked to increased short-term relapse rates (Iuliano et al., 2008) and long-term persistence of residual disability (Lublin et al., 2003; Vercellino et al., 2009). It has been shown that high relapse activity early in the course of the disease, despite active treatment, is associated with poor long-term physical outcomes (Bermel et al., 2013; Goodin et al., 2012), suggesting that severe relapses are associated with a higher risk of residual disability (Vercellino et al., 2009) and objective worsening (Hirst et al., 2008). Therefore, reducing the risk of relapses is crucial for preventing disability worsening.

Severe relapses require corticosteroid treatment as first-line and therapeutic plasma exchange as second-line treatment in corticosteroid-unresponsive patients (Ehler et al., 2017). In addition to hospitalization, patients may require long-term rehabilitation, which is associated with higher healthcare costs and decreased quality of life (Bevan and Gelfand 2015; Nickerson et al., 2015; Oleen-Burkey et al., 2012; Sormani et al., 2010). In the context of the emerging concept of "no evidence of disease activity" as a means for estimating treatment response, in relapses that impair functional ability and increase disability early treatment initiation with disease-modifying therapies (DMTs) should be considered that may offer better efficacy in terms of reduction of relapses and delay of disability in patients with relapsing-remitting MS (RRMS) (Bevan and Gelfand 2015).

Once-daily oral fingolimod 0.5 mg (Gilenya, Novartis Pharma AG) is the first-in-class sphingosine-1-phosphate receptor modulator approved for the treatment of adult patients with RRMS. In the 3 pivotal phase III studies FREEDOMS (NCT00289978), FREEDOMS II (NCT00355134), and TRANSFORMS (NCT00340834), fingolimod was shown to be highly effective on both clinical and magnetic resonance imaging (MRI) outcomes versus placebo/intramuscular (IM) interferon β-1a (IFN β-1a) (Calabresi et al., 2014; Cohen et al., 2010). Data from phase III extension studies further substantiate the long-term benefits of switching to fingolimod from placebo/IFN β-1a in preventing relapses and decreasing inflammatory activity on MRI in patients with RRMS (Cohen et al., 2016; Kappos et al., 2015; Khatri et al., 2011). In this post hoc analysis of data from phase III studies of fingolimod and their extensions, we evaluated the effect of early initiation of fingolimod on relapse severity in patients with RRMS who received continuous, long-term fingolimod treatment versus those switching to fingolimod from placebo/IFN β-1a during the extension.

2. Methods

2.1. Study design and patient population

We analyzed pooled data from the FREEDOMS/FREEDOMS II studies (n = 1556) to compare fingolimod with placebo and, in a separate analysis, data from the TRANSFORMS study (n = 860) to compare fingolimod with IFN β-1a. Detailed descriptions of the study design and patient population for each of the studies and their respective extensions have been previously published (Calabresi et al., 2014; Cohen et al., 2010; Cohen et al., 2016; Kappos et al., 2015; Kappos et al., 2010; Khatri et al., 2011; Reder 2014). Patients aged 18–55 years were eligible if they met the following inclusion criteria: diagnosis of RRMS according to the 2005 revised McDonald criteria (Polman et al., 2005); evidence of a relapsing-remitting course; one or more documented relapses in the previous year, or two or more documented relapses in the previous 2 years; an Expanded Disability Status Scale (EDSS) score of 0–5.5; and neurologically stable condition (no relapse or steroid treatment within 30 days prior to randomization). All patients provided written informed consent before participation in the studies. Each trial site obtained approval from its respective institutional review board, independent ethics committee, or research ethics board. These studies were performed in accordance with the International Conference on Harmonisation-Good Clinical Practice guidelines and the principles of the Declaration of Helsinki.

FREEDOMS and FREEDOMS II were double blind, placebo-controlled, parallel-group studies; patients were randomized (1:1:1) to fingolimod (0.5 or 1.25 mg) or placebo for 24 months. During the extension phase (Years 3–4), patients either continued to receive the same dose of fingolimod as assigned in the core phase (immediate fingolimod group) or were switched (1:1) from placebo to fingolimod 0.5 or 1.25 mg (delayed fingolimod group). TRANSFORMS was a double blind, active, comparator-controlled, parallel-group study; patients were randomized (1:1:1) to fingolimod (0.5 or 1.25 mg) or IFN β-1a IM (30 μg) for 12 months. In the extension study (Year 2), patients either continued on the same dose of fingolimod as assigned in the core phase (immediate fingolimod group) or were switched from IFN β-1a IM to fingolimod 0.5 or 1.25 mg (delayed fingolimod group). Following approval of fingolimod 0.5 mg in 2010, patients who were re-randomized to fingolimod 1.25 mg in the extension phases of FREEDOMS, FREEDOMS II and TRANSFORMS studies were switched to fingolimod 0.5 mg dose. In this post hoc analysis, we included only patients randomized to the approved dose of fingolimod 0.5 mg or to the control group. Subjects initially randomized to fingolimod 1.25 mg were excluded in the analysis.

2.2. Study evaluations

In this study, we evaluated the treatment effect of fingolimod on relapse severity in patients in the immediate fingolimod group and those in the delayed fingolimod group. Relapses were assessed by an independent evaluating physician within 7 days of symptom onset and quantified as a confirmed relapse if neurological symptoms were accompanied with a 1-point increase in at least two Functional Systems (FS) scores, or a 2-point increase in at least one FS score, or an increase of ≥0.5 points in the EDSS score. Severe relapses were defined as those exceeding the criteria for moderate relapse (i.e., 1–2-point increase in EDSS score, or a 2-point increase in FS score in 1–2 systems, or 1-point increase in FS score in 4 or more systems). Relapses were also categorized according to their impact on patients' activities of daily living, requirement of steroid administration, and hospitalization. Assessment of relapse recovery was based on the investigators' clinical judgment, and was categorized as complete recovery (post relapse EDSS score less than or equal to pre-relapse EDSS score), partial recovery (post relapse

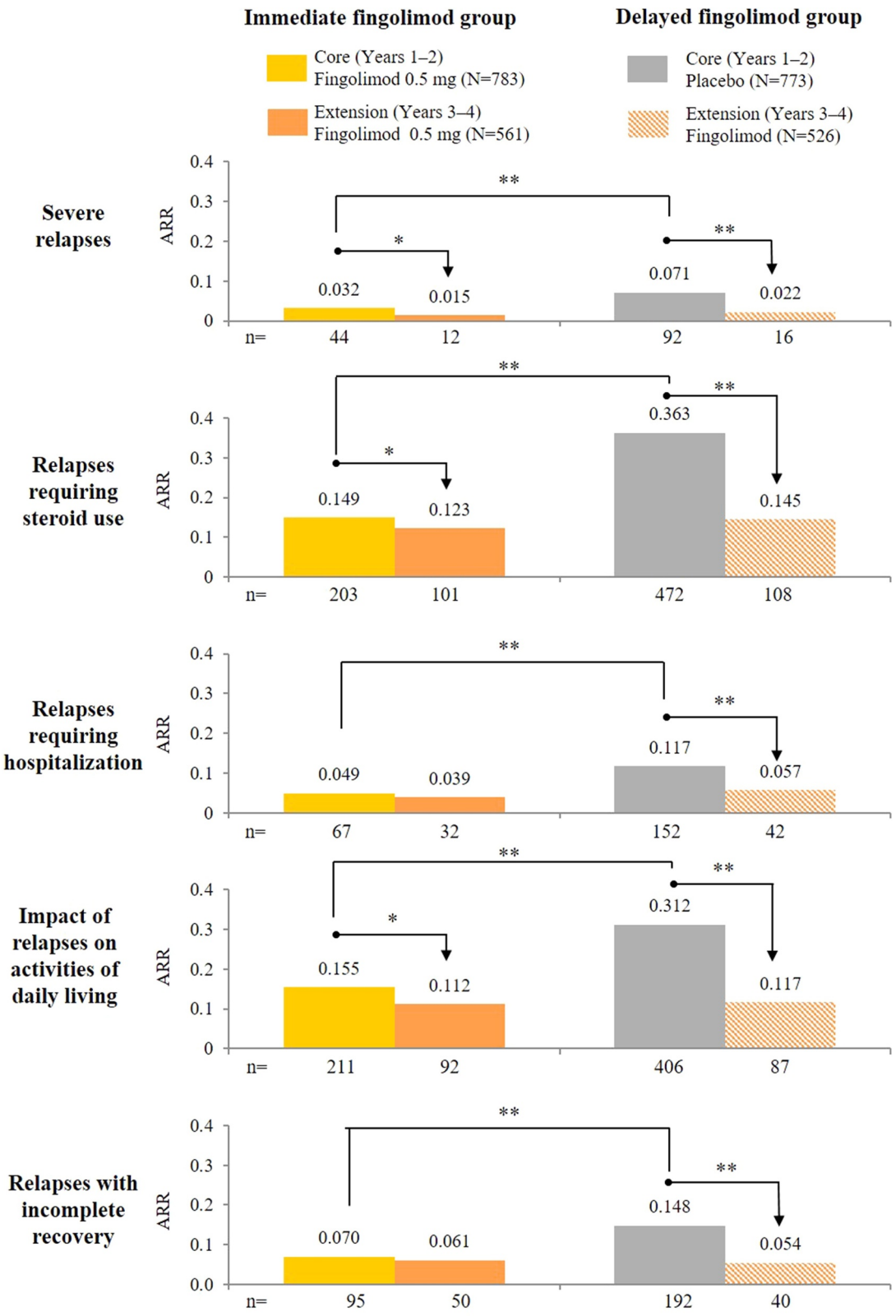

Fig. 1. Relapse severity in the immediate and delayed fingolimod groups: Pooled FREEDOMS/FREEDOMS II core and extension studies.
Crude ARRs are presented. *p*-values are from a random effects negative binomial regression model adjusted for study and period (core, extension).
*$p < 0.05$ for the within treatment group comparison of ARR for the immediate fingolimod group during the core phase (Years 1–2) and the extension phase (Years 3–4).
**$p < 0.0001$ for ARR in the between treatment comparison (fingolimod vs. placebo) during the core phase (Years 1–2) and for ARR in the within treatment group comparison for the delayed fingolimod group during the core phase (Year 1–2) and the extension phase (Years 3–4).
ARR, annualized relapse rate; N, number of patients; n, number of relapses.

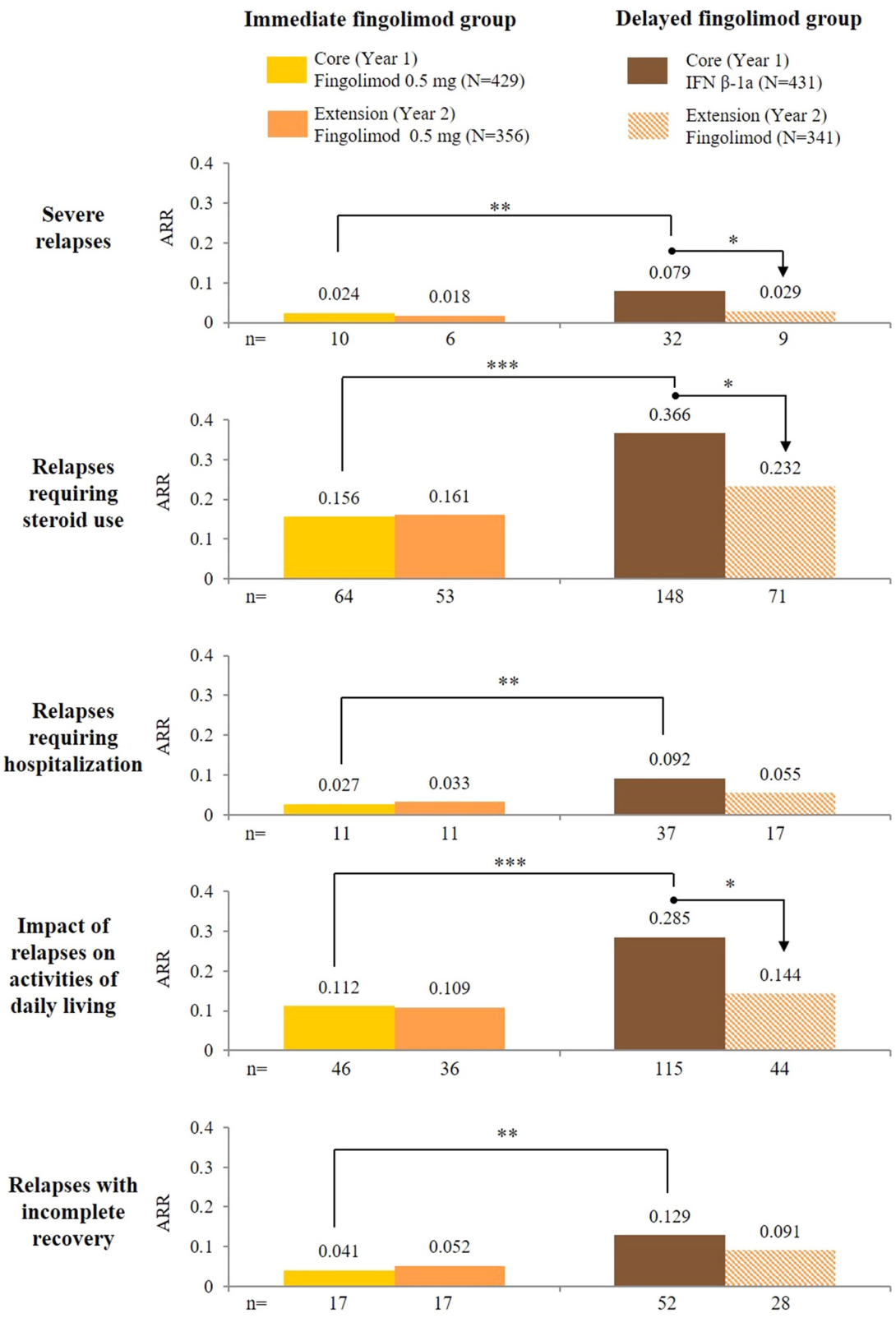

Fig. 2. Relapse severity in the immediate and delayed fingolimod groups: TRANSFORMS core and extension studies.
Crude ARRs are presented. *p*-values are from a random effects negative binomial regression model adjusted for study and period (core, extension).
*$p < 0.05$ for ARR in the within treatment group comparison for the delayed fingolimod group during the core phase (Year 1) and the extension phase (Year 2).
**$p < 0.005$ and ***$p < 0.0001$ for ARR in the between treatment comparison (fingolimod vs. IFN β−1a) during the core phase (Year 1).
ARR, annualized relapse rate; IFN β−1a, interferon β−1a; N, number of patients; n, number of relapses.

EDSS score less than EDSS score during relapse, but greater than pre-relapse EDSS score), or no recovery (post relapse EDSS score greater than or equal to EDSS score during relapse). The investigators considered recovery from relapses as the "end date of relapse symptoms". The annualized relapse rate (ARR) was estimated for severe relapses, relapses treated with steroid administration, relapses requiring hospitalization, the impact of relapses on activities of daily living, and relapses with incomplete recovery.

2.3. Statistical analysis

The number of confirmed severe relapses, relapses requiring use of steroids, relapses leading to hospitalization, and impact of relapses on activities of daily living were descriptively summarized. Crude ARRs for any treatment group and relapse category were calculated as: (total number of relapses/total number of observation days) * 365.25. Crude ARRs are presented in subsequent figures. Model-based ARRs for all relapse categories were estimated using a negative binomial regression model adjusted for study, treatment, number of relapses in 2 years prior to baseline, and baseline EDSS score as covariates. The p-values for differences in ARRs within treatment groups and between different periods were obtained from a negative binomial model with study and observational period (core and extension phase) as fixed effects and subject as a random effect. The natural log of the annualized time in the observational period (years) was used as the offset.

3. Results

3.1. Patient baseline demographics

Patient demographics and baseline disease characteristics were similar across the treatment groups and were representative of previously reported RRMS patient populations (Calabresi et al., 2014; Cohen et al., 2010, 2016; Kappos et al., 2015; Kappos et al., 2010; Khatri et al., 2011; Reder, 2014). In the FREEDOMS and FREEDOMS II core studies, 773 patients received placebo and 783 received fingolimod 0.5 mg during the core phase. A total of 1087 patients entered the 2-year extension phase, with 561 patients in the immediate fingolimod group and 562 patients in the delayed fingolimod group. In the TRANSFORMS study, of the randomized patients included in this analysis, 429 were treated with fingolimod 0.5 mg and 431 received IFN β−1a. A total of 697 patients entered the extension phase, with 356 patients in the immediate fingolimod group and 341 patients in the delayed fingolimod group. In FREEDOMS and TRNSFORMS studies, higher proportion of patients (more than 50%) entering the study were treatment naive, while in FREEDOMS II, nearly 75% of the patients were given previous treatment including interferons, glatiramer acetate and natalizumab.

3.2. Relapse severity

In the pooled FREEDOMS/FREEDOMS II studies, at Year 2 in the core study, patients in the immediate fingolimod group showed significant reductions across all ARR categories compared with those in the placebo group ($p < 0.0001$ for all) (Fig. 1); ARR remained low up to 4 years for all categories of relapses. During the extension phase of both studies, the ARRs were significantly lower for severe relapses (= 0.0453), relapses requiring steroid use ($p = 0.0373$), and impact of relapses on activities of daily living ($p = 0.0090$) compared to core phase in patients in immediate fingolimod group (Fig. 1). Patients in the delayed fingolimod group showed much stronger reductions in all categories of relapses at Years 3–4 after switching to fingolimod following 2 years of treatment with placebo ($p < 0.0001$ for all) (Fig. 1).

In TRANSFORMS, patients in the immediate fingolimod group had significantly lower ARRs compared to patients treated with IFN β−1a (Fig. 2) for all relapse categories at Year 1 ($p < 0.005$ for all). Patients in the delayed group showed stronger reductions in all relapse categories at Year 2 after switching to fingolimod following 1 year of IFN β−1a treatment. These reductions in ARR were statistically significant for severe relapses ($p = 0.0118$), relapses requiring steroid use ($p = 0.0023$), and impact of relapses on activities of daily living ($p = 0.0002$). A non-significant trend was observed in relapses requiring hospitalization (Fig. 2).

3.3. Relapse characteristics

The proportion of relapses rated as severe in the immediate fingolimod group of the pooled FREEDOMS/FREEDOMS II studies was lower during the extension phase compared with the core phase (9.3% vs. 15.8%) (Fig. 3A). A similar trend was observed in the delayed fingolimod group with a lower proportion of severe relapses during the

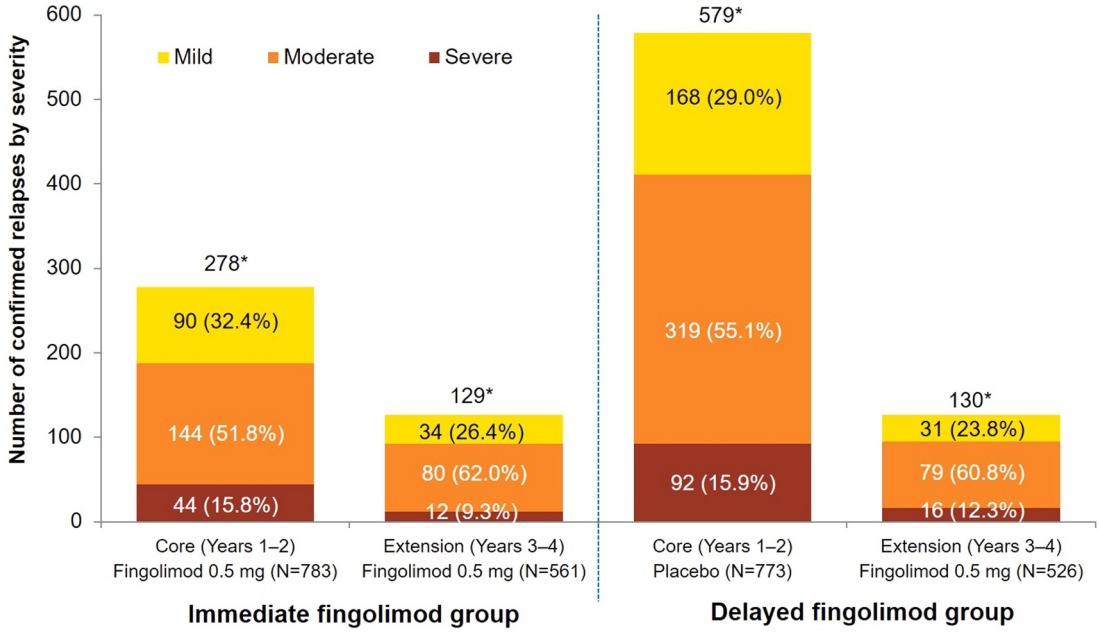

Fig. 3A. Relapse characteristics in the immediate and delayed fingolimod groups: Pooled FREEDOMS/FREEDOMS II core studies and extension studies.

extension phase compared with the core phase (12.3% vs. 15.9%). In the TRANSFORMS study, patients in immediate fingolimod group consistently had a lower proportion of severe relapses compared with patients in the IFN β−1a group, and continued to have fewer severe relapses in Year 2 compared with Year 1 (9.8% vs. 11.8%). In the delayed fingolimod group, the proportion of severe relapses decreased substantially after switching from IFN β−1a to fingolimod in Year 2 compared with Year 1 (11.1% vs. 18.0%) (Fig. 3B).

3.4. Impact of relapses and relapse recovery

In the pooled FREEDOMS/FREEDOMS II studies, the percentage of relapses that affected activities of daily living was lower in both the immediate and delayed fingolimod groups during Years 3–4 than during Years 1–2 (immediate group: 71.3% vs. 75.9% and delayed group: 66.9% vs. 70.3%). In both the immediate and delayed fingolimod groups, although the proportion of relapses requiring steroid use or hospitalization was increased during the extension phase, the overall absolute number of relapses decreased substantially (Table 1). Similar trends were observed in the TRANSFORMS study; the proportion of relapses affecting patient's activities of daily living, requiring steroid use and hospitalization in the immediate fingolimod group increased in the extension phase. In the delayed fingolimod group, the proportion of relapses requiring management using steroids and with hospitalization increased and those affecting activities of daily living decreased during the extension phase (Table 1).

The majority of patients with confirmed relapses (60–80%) showed complete recovery across all groups in both the pooled FREEDOMS/FREEDOMS II and TRANSFORMS studies and their extensions (Fig. 4A and B). In the TRANSFORMS study, more patients in the immediate fingolimod group recovered from relapses (80.0%) compared with patients in the delayed fingolimod group (70.8%).

4. Discussion

In this post-hoc analysis of the data from phase III studies of fingolimod and their extensions, we evaluated the effect of fingolimod 0.5 mg on relapse severity in patients with RRMS who were continuously treated (immediate group) and in those who switched to fingolimod during the extension phases (delayed group). Overall, the immediate fingolimod group had significantly lower ARRs for all relapse categories compared with the placebo or IFN β−1a group. In the delayed fingolimod group, larger reductions in all relapse categories were observed after switching to fingolimod from placebo/IFN β−1a during the extension. The safety of fingolimod was consistent with the established safety profile of the drug with no new safety concerns.

The long-term efficacy of fingolimod in patients with RRMS has been demonstrated in both clinical trials and in the real-world setting (Bergvall et al., 2014a,b; Kappos et al., 2015; Khatri et al., 2011; Meng et al., 2015; Reder 2014). Fingolimod was shown to reduce relapse rates versus placebo/IFN β−1a in patients with high disease activity despite previous DMT therapy and in patients with rapidly evolving severe RRMS (Cohen et al., 2013; Devonshire et al., 2012; Goodin et al., 2013). The long-term clinical benefits of fingolimod in terms of reduction in ARR were sustained for up to 4.5 years (TRANSFORMS) and 4 years (FREEDOMS II), in patients who switched from IFN β−1a or placebo to fingolimod, respectively, during the extensions phase (Cohen et al., 2016; Kappos et al., 2015; Reder 2014). Our analyses extend previous observations and demonstrate that patients receiving long-term fingolimod treatment show sustained reductions in ARR for severe relapses, relapses requiring steroid use, and relapses affecting daily activities.

Some of the major determinants of effective treatment in RRMS patients are relapse frequency, relapse severity, and degree of recovery from relapses. It has been shown that high relapse severity early in the MS disease course is associated with an increased risk of disability accumulation over a long-term period (Vercellino et al., 2009). Functional recovery from severe relapse is not always complete, and such incomplete recovery from relapse may result in disability accrual (Lublin 2007). In the present analysis, patients in the immediate fingolimod group had fewer severe relapses and the beneficial effect of treatment was sustained in the long term, with relapse rates remaining low during the extension phase. Reductions in relapse rates in the delayed fingolimod group were more pronounced after switching to fingolimod from placebo or IFN during the extension phase. In addition, reductions in ARR were significant for all relapse categories after switching from IFN-β−1a to fingolimod, indicating the potential benefits of fingolimod treatment in patients with RRMS when first-line DMTs fail. However, it should be noted that the difference in the

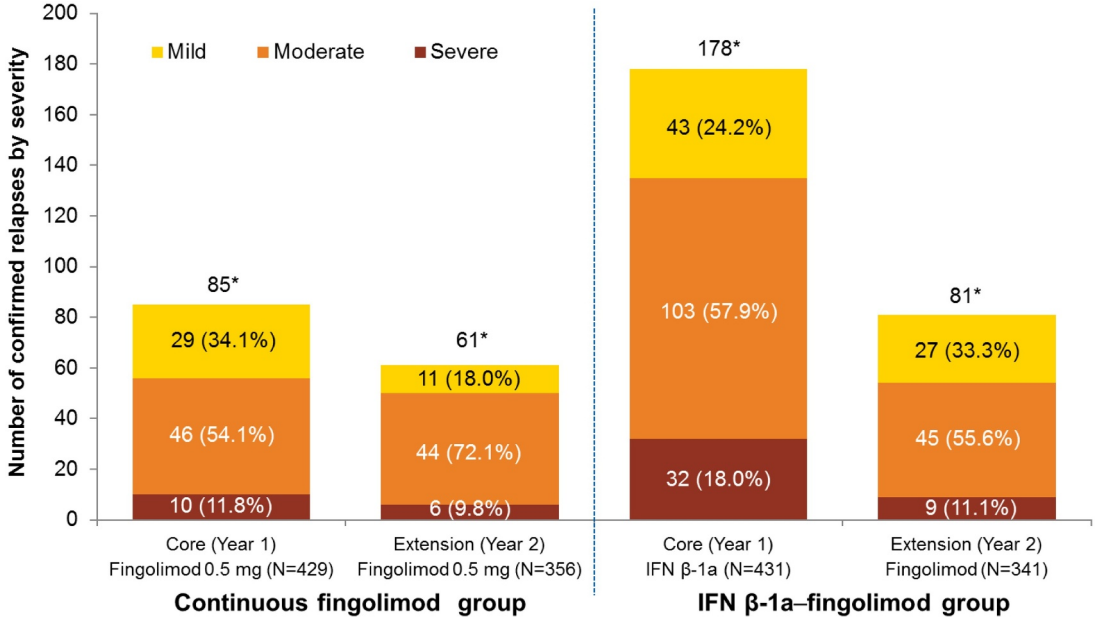

Fig. 3B. Relapse characteristics in the immediate and delayed fingolimod groups: TRANSFORMS core study and extension studies.
*Total number of confirmed relapses. Percentages were calculated using the total number of confirmed relapses as the denominator
IFN β−1a, interferon β−1a; N, number of subjects in the treatment group.

Table 1
Impact of relapses.

Pooled FREEDOMS/FREEDOMS II extensions				
Relapse impact on	Immediate fingolimod group		Delayed fingolimod group	
	Core phase (Years 1–2) Fingolimod 0.5 mg (*N* = 783)	Extension phase (Years 3–4) Fingolimod 0.5 mg (*N* = 561)	Core phase (Years 1–2) Placebo (*N* = 773)	Extension phase (Years 3–4) Fingolimod (*N* = 526)
Activities of daily living	211/278 (75.9)	92/129 (71.3)	407/579 (70.3)	87/130 (66.9)
Required steroid use	203/278 (73.0)	101/129 (78.3)	473/579 (81.7)	108/130 (83.1)
Hospitalization	67/278 (24.1)	32/129 (24.8)	152/579 (26.3)	42/130 (32.3)
TRANSFORMS extension				
Relapse impact on	Immediate fingolimod group		Delayed fingolimod group	
	Core phase (Year 1) Fingolimod 0.5 mg (*N* = 429)	Extension phase (Year 2) Fingolimod 0.5 mg (*N* = 356)	Core phase (Year 1) IFN β−1a (*N* = 431)	Extension phase (Year 2) Fingolimod (*N* = 341)
Activities of daily living	46/85 (54.1)	36/61 (59.0)	115/178 (64.6)	44/81 (54.3)
Required steroid use	64/85 (75.3)	53/61 (86.9)	148/178 (83.1)	71/81 (87.7)
Hospitalization	11/85 (12.9)	11/61 (18.0)	37/178 (20.8)	17/81 (21.0)

All values are n/m (%) where n is the number of relapses and m is the total number of confirmed relapses. Percentages were calculated using the total number of confirmed relapses as the denominator.
IFN β−1a, interferon β−1a.

reductions in relapse categories between immediate and delayed fingolimod groups were numerically smaller during the extension phase and were more likely not significant.

While relapses remain an important aspect of MS, literature on the severity of relapses in patients with MS is sparse. Patients with poor recovery from early relapses tend to develop a progressive disease course earlier than those with good recovery (Novotna et al., 2015). In practice, relapse assessments are often subjective and may result in overlooked symptoms, unaddressed patient concern, unnoticed or under recognized side effects of therapies, and suboptimal therapeutic response (Ross et al., 2012). Therefore, it is important to consider the clinical relevance of relapses as an outcome and initiate high-efficacy therapies early to delay the progression and minimize disability in patients experiencing severe exacerbations. In our analysis, patients in immediate fingolimod group showed improved relapse outcomes over the long term. In a retrospective analysis comparing the effect of switching to either oral fingolimod, injectable IFN β−1a, or glatiramer acetate, switching to fingolimod was more effective in controlling relapse activity and accumulation of disability compared to other injectable DMTs (He et al., 2015). In a post hoc analysis of the TRANSFORMS extension, the median time to first confirmed relapse was approximately doubled in patients who switched from IFN β−1a to fingolimod compared with continued IFN β−1a treatment (Meng et al., 2015). In a subgroup analysis of the TRANSFORMS study, patients who switched from IFN β−1a to fingolimod 0.5 mg at the start of the extension phase showed relative reductions in ARR of 30% compared with the previous 12-month core phase (Khatri et al., 2011). In an earlier subgroup analysis of pooled data from 3 phase III studies, fingolimod was associated with consistent reductions in ARR among young, treatment-naïve patients with low levels of disability based on their EDSS score at baseline. This, again, suggests that patients withinitiatin RRMS may incur greater treatment benefits when initiated on fingolimod

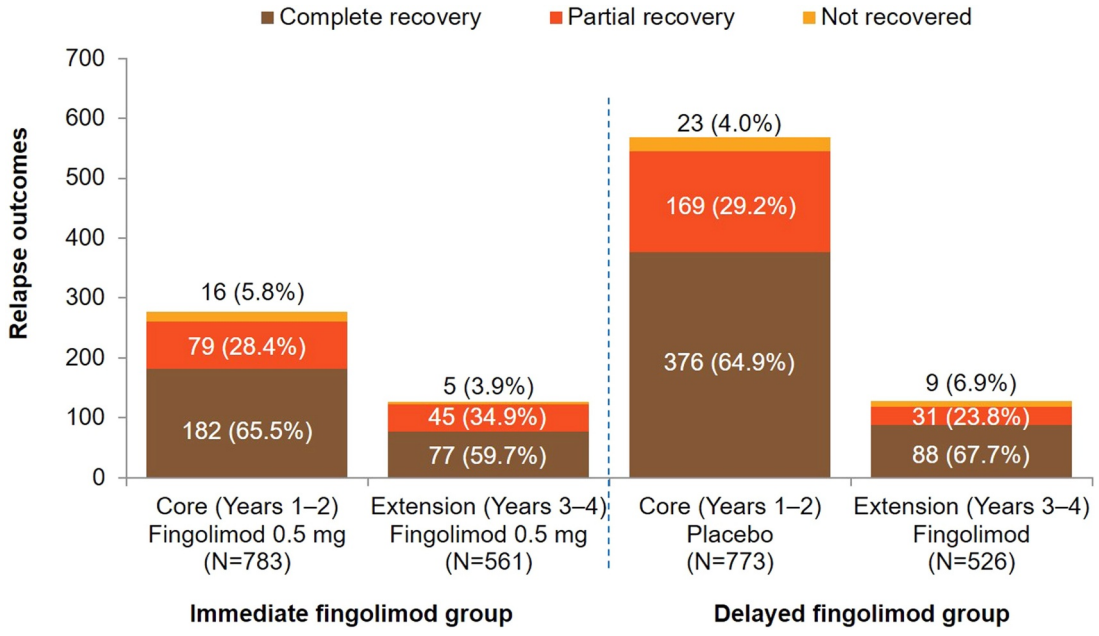

Fig. 4A. Pooled FREEDOMS/FREEDOMS II extensions: Relapse recovery in the immediate and delayed fingolimod groups.

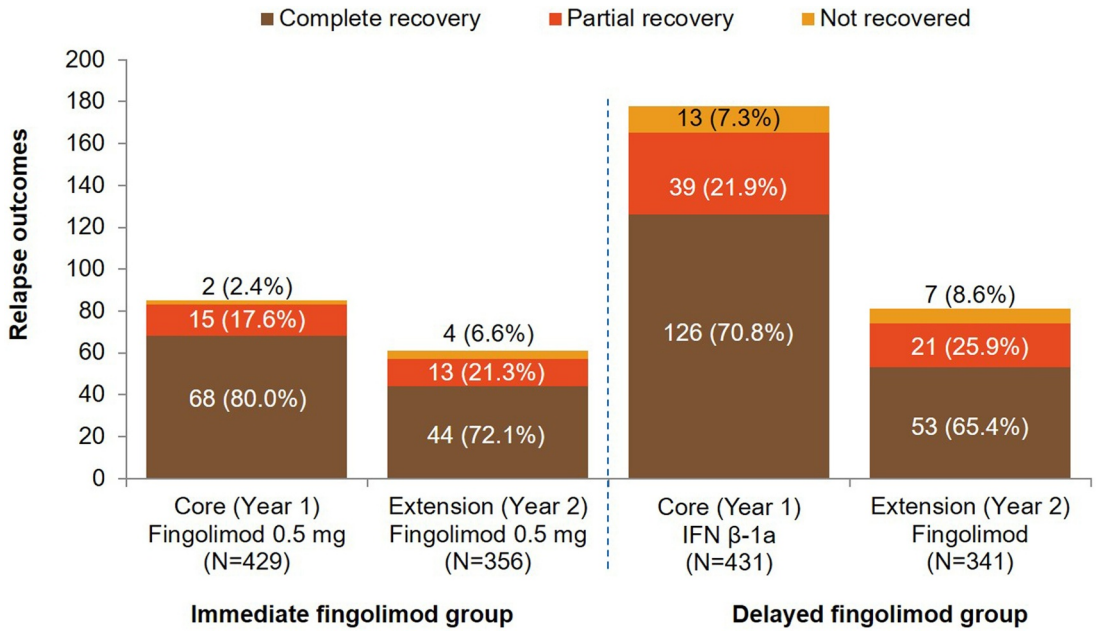

Fig. 4B. TRANSFORMS extension: Relapse recovery in the immediate and delayed fingolimod groups.
All values are n (%) where n represents the number of relapses and the values in brackets represent the percentage of relapses. Percentages were calculated using the total number of confirmed relapses as the denominator (m). Percentages may not add up to 100% as the relapses with unknown outcomes/missing are not shown because of small numbers. IFN β−1a, interferon β−1a.

therapy early in the course of the disease (Derfuss et al., 2016). Results from real-world studies for RRMS have also demonstrated the benefits of fingolimod in reducing relapse rates compared with commonly used first-line treatments (Bergvall et al., 2014a,b; He et al., 2015; Roskell et al., 2012). One of the limitations associated with this pooled analysis is potential bias resulting from drop-out of patients experiencing lack of efficacy during the core and extension phases. Given the longer duration of the study, it may be assumed that treatmenteffect among the drop-outs was lower and that patients who discontinued tended to have higher disease activity while on study compared to the completers (Cohen et al., 2016). In a sub group analyses of non-completers in the TRANSFORMS study, patients who were initially randomized to fingolimod had a lower ARR than those who had been randomized to IFN in the core study, confirming the benefits of early initiation of fingolimod treatment for relapse control (Cohen et al., 2016).

Patients with RRMS experience restrictions in daily activities and reduced functional ability, resulting in compromised health-related quality of life, eventually leading to increased economic burden (Halper 2007; Kalb 2007; Oleen-Burkey et al., 2012). Severe relapses lead to higher healthcare resource utilization and cost, which contributes to the significant economic burden for patients with RRMS (Raimundo et al., 2013). The cost of managing a relapse in the inpatient care setting in the United States was estimated to be 6 times higher than the cost of managing a relapse in an outpatient setting (O'Brien et al., 2003). In our study, patients in the delayed fingolimod group reported higher use of steroids during the extension phase when compared to the immediate fingolimod group. This may be explained by the higher rates of severe relapses in these patients despite being treated with active therapy. While the use of short-term, high-dose corticosteroids is a common approach for treating severe relapses (Ciccone et al., 2008; Ross et al., 2013), patients treated with corticosteroids are at an increased risk of side effects, with palpitations, flushing, dyspepsia, insomnia, dysgeusia, and sinusitis being the most frequently reported (Lattanzi et al., 2017; Shaygannejad et al., 2013). According to the North American Research Committee on Multiple Sclerosis (NARCOMS) registry, 40% of the most recent relapses were left untreated, reflecting patient dissatisfaction with corticosteroid therapy due to adverse events (Nickerson and Marrie 2013). In addition, evidence suggests that despite active treatment, more than 50% of patients with RRMS experience clinical worsening over a decade of observation, resulting in disability accrual in the long term (Cree et al., 2016). In this context, early treatment initiation with a high-efficacy DMT that may reduce the rates of severe relapse early in the disease course while avoiding adverse side effects is a valuable option.

5. Conclusions

In summary, a relapse serves as an important indicator of MS disease activity, and treatments that reduce the frequency and severity of relapses are central to the management of RRMS. Our analysis of data from the 3 pivotal phase III studies of fingolimod (FREEDOMS, FREEDOMS II, and TRANSFORMS) demonstrates that early initiation of fingolimod treatment was associated with reduction in the proportion of severe relapses and with sustained long-term benefits. The clinical benefits observed in patients with RRMS underscores the importance of initiating fingolimod treatment early during the disease course, i.e. in patients with signs of disease activity, for favorable long-term prognoses.

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Conflict of interest

Judith Haas has received compensation from Almiral, Biogen, Bayer, Octapharma, Teva, Allergan and Novartis.

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Diego Silva was an employee of Novartis Pharma AG at the time of preparation of the manuscript.

Daniela Piani Meier is an employee of Novartis Pharma AG, and **Rolf Meinert** is an employee of DATAMAP GmbH, Freiburg, Germany, which provides services to Novartis Pharma AG.

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