Fingolimod in the treatment of relapsing–remitting multiple sclerosis: long-term experience and an update on the clinical evidence

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***Abstract*:** Since the approval in 2010 of fingolimod 0.5 mg (Gilenya; Novartis Pharma AG, Basel, Switzerland) in the USA as an oral therapy for relapsing forms of multiple sclerosis, long-term clinical experience with this therapy has been increasing. This review provides a summary of the cumulative dataset from clinical trials and their extensions, plus postmarketing studies that contribute to characterizing the efficacy and safety profile of fingolimod in patients with relapsing forms of multiple sclerosis. Data from the controlled, phase III, pivotal studies [FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis), FREEDOMS II and TRANSFORMS (Trial Assessing Injectable Interferon *versus* FTY720 Oral in Relapsing–Remitting Multiple Sclerosis)] in relapsing–remitting multiple sclerosis have shown that fingolimod has a robust effect on clinical and magnetic resonance imaging outcomes. The respective study extensions show that effects on annualized relapse rates are sustained with continued fingolimod treatment. Consistent, significant reductions in magnetic resonance imaging lesion counts and brain volume loss have also been sustained with long-term treatment. The safety profile of fingolimod is also examined, particularly in light of its long-term use. A summary of the adverse events of interest that are associated with fingolimod treatment and associated label guidelines are also considered, which include cardiac effects following first-dose administration, infections, lymphopenia, macular edema and pregnancy. Historic hurdles to the prescription of fingolimod and how these challenges are being met are also discussed.

Keywords: clinical experience, fingolimod, long-term efficacy, multiple sclerosis, safety

Introduction

Fingolimod 0.5 mg (Gilenya; Novartis Pharma AG, Basel, Switzerland) is a sphingosine 1-phosphate (S1P) receptor modulator and was the first oral therapy to be approved for multiple sclerosis (MS), receiving a broad first-line indication for relapsing forms of MS (RMS) in the USA in 2010 [Food and Drug Administration, 2010, 2015]. It was approved in the European Union (EU) in March 2011 for patients with highly active relapsing–remitting MS (RRMS) [European Medicines Agency, 2011]. Combining the populations in the clinical trial and postmarketing settings, approximately 125,000 patients have been treated with fingolimod and total patient exposure now exceeds 240,000 patient years [Novartis, 2015b].

Efficacy and safety findings from study extensions, postmarketing studies and real-world patient populations all contribute towards the cumulative clinical evidence for the benefit of fingolimod. This review presents a summary of the long-term experience with fingolimod and provides an insight on the practical use of this disease-modifying therapy (DMT) in the clinic, including the impact of revisions to the US label.

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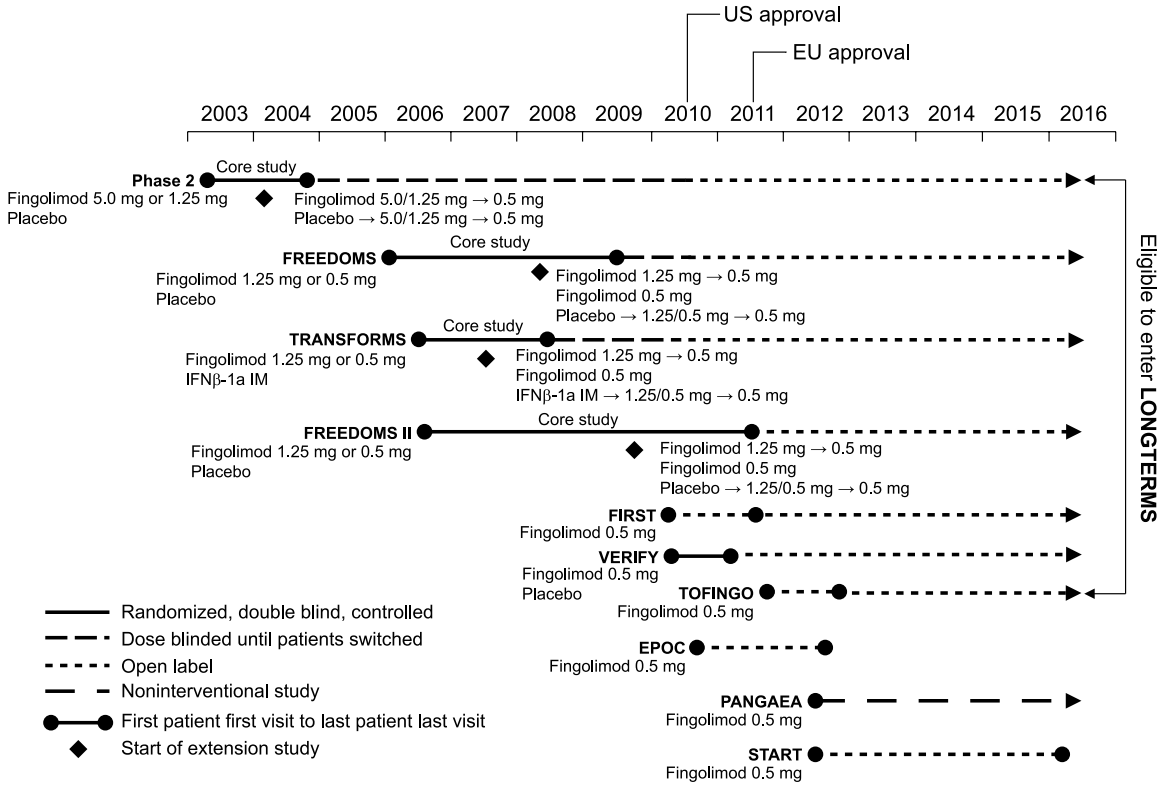

Figure 1. Clinical development program of fingolimod and key postmarketing studies.
EPOC, Evaluate Patient OutComes; FIRST, Fingolimod Initiation and Cardiac Safety Trial; FREEDOMS, FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis; IFNβ-1a IM, intramuscular interferon β-1a; PANGAEA, Post-Authorization Non-interventional German sAfety of GilEnyA in RRMS patients; START, STudy to vAlidate telemetRic ECG Systems for firsT Dose Administration of Fingolimod; TOFINGO, Disease Control and Safety in Patients With RRMS Switching From Natalizumab to Fingolimod; TRANSFORMS, Trial Assessing Injectable Interferon *versus* FTY720 Oral in Relapsing–Remitting Multiple Sclerosis; VERIFY, Investigating the effect of recent immunization in patients receiving fingolimod therapy.

Breadth and depth of clinical experience with fingolimod

Following the approval of fingolimod 0.5 mg in the USA and Europe [Food and Drug Administration, 2010; European Medicines Agency, 2011], efficacy and safety data generated in the postmarketing setting have complemented and extended data from the phase II and pivotal phase III studies. The clinical development program of fingolimod (Figure 1) illustrates how evidence from real-world studies and long-term trials provides a supporting source of information to help inform physicians when tailoring individual patient treatment pathways.

Patients in the phase II study initially received 5 mg and 1.25 mg doses of fingolimod, but were switched to the 0.5 mg dose during the extension study [Kappos *et al.* 2006]. Subsequently, three phase III studies were conducted in patients with RRMS using the approved fingolimod 0.5 mg dose. FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis) [Kappos *et al.* 2010] and FREEDOMS II [Calabresi *et al.* 2014] were randomized, double-blind, multicenter, controlled, 24-month trials *versus* placebo, TRANSFORMS (Trial Assessing Injectable Interferon *versus* FTY720 Oral in Relapsing–Remitting Multiple Sclerosis) was a 12-month, double-blind, controlled study *versus* intramuscular interferon β-1a (IFNβ-1a) [Cohen *et al.* 2010]. Each of these three studies has reported data from their respective extension studies [O'Connor *et al.* 2009; Comi *et al.* 2010; Khatri *et al.* 2011; Antel *et al.* 2012; Reder *et al.* 2013; Vollmer *et al.* 2013; Cohen *et al.* 2015a; Kappos *et al.* 2015b]. The long-term safety and efficacy of fingolimod are being investigated in the LONGTERMS study, an ongoing open-label, single-arm, long-term extension of phase II/III/IIIb trials of fingolimod [Radue *et al.* 2014a; Cohen *et al.* 2015b]. In addition, the ACROSS (A CROsS-Sectional) study aims to report 10-year clinical and imaging data from around 90% of the

phase II intent-to-treat population. Other post-marketing studies that provide safety and efficacy data to broaden the experience of fingolimod in RMS include the phase IIIb, open-label, 4-month FIRST (Fingolimod Initiation and caRdiac Safety Trial) study [Gold *et al.* 2014], the phase IV, open-label, 6-month EPOC (Evaluate Patient OutComes) study [Fox *et al.* 2014; Hughes *et al.* 2014], the START (STudy to vAlidate telemetRic ECG Systems for firsT dose administration of fingolimod) study – a prospective, 1-week, multicenter, open-label study of up to 7000 patients with RRMS across Germany [Limmroth *et al.* 2015] – and the prospective, multicenter, noninterventional, long-term PANGAEA (Post-Authorization Non-interventional German sAfety of GilEnyA in RRMS patients) study [Ziemssen *et al.* 2015a]. Additional postmarketing information relating to switching to fingolimod from other therapies includes the randomized, placebo-controlled TOFINGO (disease control and safety in patients with RRMS switching from natalizumab TO FINGOlimod) study [Kappos *et al.* 2015c], the randomized, placebo-controlled vaccination VERIFY (inVestigating the Effect of Recent Immunization in patients receiving Fingolimod therapy) study [Kappos *et al.* 2015a], the global, observational MSBase registry [He *et al.* 2015] and evidence from a US claims database [Bergvall *et al.* 2014b].

The efficacy and safety of fingolimod 0.5 mg has been investigated in patients with primary progressive MS (PPMS) in the INFORMS (INvestigating FTY720 ORal in Primary Progressive MS) trial. This was a multicenter, double-blind, placebo-controlled, randomized, parallel-group trial, during which patients received study drug or placebo for at least 3 years [Lublin *et al.* 2015].

Efficacy of fingolimod

Effect of fingolimod treatment on relapse rates and disability progression

Data from the pivotal phase III studies show that fingolimod has a robust effect in patients with RRMS. The key relapse, disability and magnetic resonance imaging (MRI) results of these studies are summarized in Table 1.

Annualized relapse rate (ARR) was a primary efficacy outcome in the pivotal phase III trials of fingolimod (Table 1) [Cohen *et al.* 2010; Kappos *et al.* 2010; Calabresi *et al.* 2014]. At the approved dose of 0.5 mg once daily, treatment with fingolimod led to significant reductions in ARR *versus* comparators in the FREEDOMS (54%), FREEDOMS II (48%) and TRANSFORMS (52%) studies, respectively [Cohen *et al.* 2010; Kappos *et al.* 2010; Calabresi *et al.* 2014].

Investigations also show that fingolimod has a consistent, significant effect on ARR *versus* intramuscular IFNβ-1a across patient subgroups, regardless of prior interferon (IFN) treatment (58%), prior treatment efficacy (57%) or duration of more than 1 year (55%) or were treatment naïve (55%) [Khatri *et al.* 2014]. Similar results were seen in subgroup analysis of the FREEDOMS study [Devonshire *et al.* 2012]. Further *post hoc* subgroup analyses of FREEDOMS and TRANSFORMS data show that fingolimod is effective in reducing relapse rates early in the MS disease course. In patients with a duration of MS of less than 3 years since their first symptom, fingolimod reduced ARR by 73.4% ($p = 0.0002$) *versus* intramuscular IFNβ-1a and by 67.4% ($p < 0.0001$) *versus* placebo [Agius *et al.* 2014].

As well as having an effect in patients early in the MS disease course, recent analysis of data from the three pivotal studies demonstrates that disease activity (relapses and/or MRI outcomes) in the first year of fingolimod treatment is predictive of long-term clinical outcomes over the following 3 years of therapy [Boster *et al.* 2015; Repovic *et al.* 2015]. This indicates that early treatment is important for patients with MS, and that the early identification of patients at risk of suboptimal response to treatment is important for considering therapeutic options to optimize long-term outcomes.

A substantial dataset from extensions of the three pivotal phase III trials of fingolimod has shown that low relapse rates are sustained with continued fingolimod treatment. Over the duration of the FREEDOMS core and 2-year extension study, patients continuously receiving fingolimod had a mean ARR of 0.19 compared with 0.36 for those who had switched from placebo in the core study to fingolimod during the extension study [Kappos *et al.* 2015b]. Similarly, in the 2-year extension to FREEDOMS II, mean ARR was 0.19 for those continuously receiving fingolimod [Reder *et al.* 2013]. In the 1-year extension of TRANSFORMS, patients receiving a second year of continuous fingolimod treatment had a mean ARR of 0.11 [Khatri *et al.* 2011]. At the 4.5-year follow up of

Table 1. Key results of the pivotal phase III clinical trials of the approved 0.5 mg fingolimod dose [Cohen *et al.* 2010; Kappos *et al.* 2010; Calabresi *et al.* 2014].

Trial	Design	Study arms	Key clinical results	Key MRI results
FREEDOMS [Kappos *et al.* 2010]	mc, ran, db, pc $n = 1272$ Duration 24 months	Placebo ($n = 418$) Fingolimod 0.5 mg daily ($n = 425$) Fingolimod 1.25 mg daily ($n = 429$)	**ARR** FTY 0.18; Pbo 0.40; ARR ratio 0.46 ($p \leqslant 0.001$); relative reduction 54% **Proportion free from 3M CDP** FTY 82.3; Pbo 75.9; HR 0.70 ($p < 0.05$); relative reduction 30%	**Gd-enhancing T1 lesion count, mean** FTY 0.2; Pbo 1.1; count ratio 0.21 ($p \leqslant 0.001$); relative reduction 79% **New/newly enlarged T2 lesion count, mean** FTY 2.5; Pbo 9.8; count ratio 0.26 ($p \leqslant 0.001$); relative reduction 74% **Percent change in T1 hypointense lesion volume from baseline, mean** FTY 50.7%; Pbo 8.8% ($p = 0.012$); relative reduction 82.6% **Percent change in brain volume from baseline, mean** FTY –0.8; Pbo –1.3; relative reduction 36% ($p < 0.001$)
TRANSFORMS [Cohen *et al.* 2010]	mc, ran, db, pc $n = 1292$ Duration 12 months	IFNβ-1a 30 µg intramuscularly weekly ($n = 431$) Fingolimod 0.5 mg daily ($n = 429$) Fingolimod 1.25 mg daily ($n = 420$)	**ARR** FTY 0.16; IFN 0.33; ARR ratio 0.48 ($p \leqslant 0.001$); relative reduction 52% **Proportion free from 3M CDP** FTY 94.1; IFN 92.1; HR 0.71 ($p =$ NS); relative reduction 29%	**Gd-enhancing T1 lesion count, mean** FTY 0.2; IFN 0.5; count ratio 0.46 ($p < 0.01$); relative reduction 54% **New/newly enlarged T2 lesion count, mean** FTY 1.5; IFN 2.1; count ratio 0.75 ($p < 0.05$); relative reduction 25% **Percent change in T1 hypointense lesion volume from baseline, mean** FTY 24.1%; IFN 15.0% ($p =$ NS); relative reduction 37.8% **Percent change in brain volume from baseline, mean** FTY –0.3; IFN –0.5; relative reduction 31% ($p < 0.001$)
FREEDOMS II [Calabresi *et al.* 2014]	mc, ran, db, pc, $n = 1083$ Duration 24 months	Placebo ($n = 355$) Fingolimod 0.5 mg daily ($n = 358$) Fingolimod 1.25 mg daily ($n = 370$)	**ARR** FTY 0.21; Pbo 0.40; ARR ratio 0.52 ($p \leqslant 0.0001$); relative reduction 48% **Proportion free from 3M CDP** FTY 74.7; Pbo 71.0; HR 0.83 ($p =$ NS); relative reduction 17%	**Gd-enhancing T1 lesion count, mean** FTY 0.4; Pbo 1.2; count ratio 0.30 ($p < 0.05$); relative reduction 70% **New/newly enlarged T2 lesion count, mean** FTY 2.3; Pbo 8.9; count ratio 0.26 ($p < 0.05$); relative reduction 74% **Percent change in T1 hypointense lesion volume from baseline, mean** FTY 12.6%; Pbo 26.4% ($p =$ NS); relative reduction 52.1% **Percent change in brain volume from baseline, mean** FTY –0.9; Pbo –1.3; relative reduction 31% ($p < 0.001$)

3M, 3 month; ARR, annualized relapse rate; CDP, confirmed disability progression; db, double blind; FREEDOMS, FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis; FTY, fingolimod; Gd, gadolinium; HR, hazard ratio; IFN, interferon; mc, multicenter; NS, nonsignificant; Pbo, placebo; pc, placebo controlled; ran, randomized; TRANSFORMS, Trial Assessing Injectable Interferon *versus* FTY720 Oral in Relapsing–Remitting Multiple Sclerosis.

TRANSFORMS, patients who received continuous fingolimod treatment for up to 4.5 years had a significantly lower ARR compared with those in the IFNβ-1a-switch group (0.17 *versus* 0.27), with an associated 35% reduction in the risk of relapse ($p < 0.001$) [Cohen *et al.* 2015a]. At the end of the 7-year phase II extension study, ARR was low and sustained at 0.16 for patients who continuously received fingolimod ($n = 87$) compared with 0.21 in the placebo-switch patients ($n = 83$) [Antel *et al.* 2012]. Patients in this study received higher than approved doses of fingolimod for up to 5 years of the 7-year study (5.0 mg/1.25 mg then 1.25 mg) before switching to the 0.5 mg dose [Antel *et al.* 2012].

Finally, an interim analysis of the prospective, multicenter, noninterventional, long-term PANGAEA study of more than 3900 patients reported a significant reduction in mean ARR by 75% from 1.50 at baseline to 0.37 after 3 years of fingolimod treatment ($p < 0.001$); this rate was unaffected by previous treatment with IFN, glatiramer acetate or natalizumab [Ziemssen *et al.* 2015b].

Assessment of long-term disability status is important for characterizing the benefit–risk profile of disease-modifying MS therapies. A reduction in the risk of confirmed disability progression (CDP) over 3 and 6 months was assessed in the pivotal phase III studies of fingolimod [Cohen *et al.* 2010; Kappos *et al.* 2010; Calabresi *et al.* 2014]. The effects of fingolimod on CDP in the respective overall study populations are summarized in Table 1. In FREEDOMS, a significant reduction of 30% *versus* placebo was observed in the risk of 3-month CDP ($p < 0.02$). A similar, significant reduction of 37% in risk of 6-month CDP relative to placebo was also seen ($p < 0.01$) [Kappos *et al.* 2010]. In FREEDOMS II, there was high variability in Expanded Disability Status Scale (EDSS) scores in patients with a baseline score of 0, for whom the progression rate was high across treatment groups. This may have contributed to the lack of significant effect of fingolimod on 3-month CDP in FREEDOMS II [Calabresi *et al.* 2014].

Data from the FREEDOMS extension study suggest that long-term treatment with fingolimod could have a beneficial effect on disability progression. At the end of the 2-year extension study, the proportions of patients free from 3-month and 6-month CDP were 74% and 80%, respectively [Kappos *et al.* 2015b]. Compared with the group of patients who switched from placebo to fingolimod, the respective risk of 3-month and 6-month CDP was reduced by 27% [hazard ratio (HR) 0.73; 95% confidence interval (CI) 0.56–0.95; $p = 0.0189$] and 31% (HR 0.69; 95% CI 0.51–0.93; $p = 0.0140$), respectively, in the continuous fingolimod 0.5 mg group [Kappos *et al.* 2015b].

Despite the significant effects of fingolimod on disability progression in FREEDOMS core and extension, during the TRANSFORMS extension, the time to 3-month CDP did not differ between continuous fingolimod and switch groups [Khatri *et al.* 2011], an effect that perhaps unsurprisingly remained in the 4.5-year follow up, given that both groups received fingolimod for a considerable length of time compared with the 1-year core study [Cohen *et al.* 2015a]. A trend in favor of continuous treatment with fingolimod *versus* switching from placebo was apparent for the time to 3-month CDP up to study end in the FREEDOMS II extension study; the HR for fingolimod *versus* placebo–fingolimod was 0.91 (95% CI 0.69–1.20; $p = 0.613$) [Reder *et al.* 2013].

Longitudinal analysis of EDSS scores combined from the fingolimod phase III core and extension trials showed that approximately two-thirds of patients receiving fingolimod who continued on treatment had the same or better EDSS score after 2 years (67.9%), 3 years (64.7%) and 4 years (66.8%) of treatment and 16–18% had improved EDSS scores from baseline [Cree *et al.* 2014]. However, for this *post hoc* analysis, a lack of control group and selective dropouts should be noted as this may produce bias. Nevertheless, data from PANGAEA show that, over a 3-year period, approximately 90% of patients ($n = 404$) had a stable EDSS score [Ziemssen *et al.* 2015b].

Of note, recent evaluation of disability outcomes from the MSBase cohort, based on 3–6 months of CDP on EDSS scores, suggests that the accumulation of permanent disability may be overestimated by up to 30%, which may lead to spurious estimates from short-term clinical trials [Kalincik *et al.* 2015a].

The INFORMS study of fingolimod in patients with PPMS reported no significant effect of treatment on the risk of disability progression confirmed at 3 months [Lublin *et al.* 2015; Yaldizli *et al.* 2015], which suggests that differences in underlying disease processes between RRMS and

PPMS may mean that distinct, targeted therapeutic strategies may be required for the progressive and relapsing forms of MS.

Effect of fingolimod treatment on MRI outcomes

In phase III trials, fingolimod 0.5 mg had a consistent, significant effect on MRI outcomes, namely gadolinium (Gd)-enhancing T1 lesion counts, T2 lesion counts, T1 hypointense volume change and also brain volume loss (BVL), which are summarized in Table 1 [Cohen *et al.* 2010; Kappos *et al.* 2010; Radue *et al.* 2012; Barkhof *et al.* 2014; Calabresi *et al.* 2014].

Fingolimod 0.5 mg consistently reduced the mean rate of BVL in the pivotal studies of patients with RRMS by approximately one third *versus* placebo or IFNβ-1a (Table 1), with effects observed from as early as 6 months of treatment [Cohen *et al.* 2010; Kappos *et al.* 2010; Calabresi *et al.* 2014; Radue *et al.* 2014b]. With long-term continuous fingolimod treatment, a consistent reduction in BVL with fingolimod treatment was observed when combined across core and extension studies, with BVL of 0.45% (FREEDOMS), 0.41% (FREEDOMS II) and 0.31% (TRANSFORMS). Patients who switched from core study comparators at extension study baseline had BVL reductions of 0.49% (FREEDOMS), 0.47% (FREEDOMS II) and 0.25% (TRANSFORMS), which were numerically similar to those for continuously treated patients, although no statistical comparisons were made [Radue *et al.* 2014b]. In LONGTERMS, reductions in annualized rates of BVL were sustained up to month 72 from baseline [Radue *et al.* 2014a]. No significant effect of treatment on the rate of BVL was found in the INFORMS study [Lublin *et al.* 2015; Yaldizli *et al.* 2015]. Mean percent brain volume changes from baseline to final MRI were (± standard deviation) 1.34 ± 1.22 for fingolimod *versus* 1.42 ± 1.27 for placebo ($p = 0.707$). Although the overall level of inflammatory activity in the PPMS population was low, fingolimod reduced the number of Gd-enhancing T1 lesions by 78% and of new/newly enlarged T2 lesions by 73% (both $p < 0.001$) [Lublin *et al.* 2015; Yaldizli *et al.* 2015].

The loss of brain volume is known to occur more rapidly in patients with MS (typically 0.5–1.35% per year) than in healthy, age-matched individuals without MS (0.1–0.3%) and begins early in the course of the disease [Bermel and Bakshi, 2006]. It continues throughout the course of MS, at a rate largely independent of MS subtype [De Stefano *et al.* 2010, 2015]. The relevance of reductions in BVL with fingolimod treatment has been assessed in 3635 patients from the pivotal phase III studies and their extensions; the rate of BVL correlates with disease severity at baseline and CDP has been seen in a greater proportion of patients with high rates of BVL than in those with lower rates [Radue *et al.* 2015]. Although measurement of BVL has been widely adopted as an outcome in clinical trials, it has not yet entered clinical practice in the field of MS as a standardized measure.

Nevertheless, it has been proposed that BVL, in addition to relapses, disability progression and MRI activity outcomes, can provide valuable, previously overlooked information to assess the treatment response of patients using the 'no evidence of disease activity' (NEDA) composite; a measure which is currently relevant in the clinical trial setting but may eventually find utility in patient management [Kappos *et al.* 2015d].

While definitions vary, the NEDA composite is a stringent assessment of efficacy, with reports indicating that only a minority of patients sustain NEDA over time [Rotstein *et al.* 2015]. Based on a definition of NEDA that included changes in brain volume, almost 20% of patients achieved NEDA with fingolimod therapy compared with only 5% of patients on placebo in an analysis of the pooled FREEDOMS population [Kappos *et al.* 2015d]. The aspiration of achieving NEDA status is complete disease remission, based on a more comprehensive consideration of the underlying pathology of MS than can be gained by assessment of individual outcomes, such as relapse rates.

Although the NEDA composite endpoint has the potential to capture the impact of therapies on both inflammation and neurodegeneration, it is known that neuropsychological aspects such as cognition, fatigue and depression play an important role in the quality of life of patients with MS, in addition to the more physically oriented parameters of relapse and progression of disability [Stangel *et al.* 2015]. The former are yet to be formally included in standardized measures of NEDA and future definitions will likely need to include these in addition to patient-related outcome measures (PROs or PROMs), focal grey matter disease activity and possibly

fluid biomarkers, for example cerebrospinal fluid neurofilament levels [Giovannoni *et al.* 2015].

Comparison of fingolimod efficacy with other therapies

As yet, there are no head-to-head randomized clinical trials that compare the efficacy of fingolimod with other oral therapies or with natalizumab. Data from smaller studies and *post hoc* treatment comparison studies have provided some indications of the relative efficacy of these compounds [Bergvall *et al.* 2014b; Nixon *et al.* 2014; He *et al.* 2015; Kalincik *et al.* 2015b; Warrender-Sparkes *et al.* 2015].

Analyses from MSBase, an ongoing, longitudinal, observational registry, suggest that switching to fingolimod (n = 148) is associated with fewer relapses (ARR 0.31 *versus* 0.42; 95% CI 0.02–0.19; p = 0.009), lower risk of disability progression (HR 0.53; 95% CI 0.31–0.91; p = 0.02) and greater treatment persistence than is achieved switching to injectable immunomodulators (n = 379) [He *et al.* 2015]. Retrospective evidence from a US claims database has shown that fingolimod (n = 128) is associated with a 50% reduction in ARR (rate ratio 0.50; 95% CI 0.34–0.75; p = 0.0006) compared with IFNs or glatiramer acetate (n = 397) [Bergvall *et al.* 2014b]. Additional analyses of the MSBase registry show that patients are less likely to discontinue fingolimod than injectable DMTs ($p < 0.001$), and that patients switch to fingolimod for convenience [Warrender-Sparkes *et al.* 2015].

Relapse rates and disability progression have been compared between MSBase registry patients with active RRMS who switched to fingolimod (n = 171) or to natalizumab (n = 407) [Kalincik *et al.* 2015b]. ARR decreased from 1.5 to 0.2 for patients switching to natalizumab and from 1.3 to 0.4 for patients switching to fingolimod; 50% relative post-switch difference in relapse hazard (p = 0.002) and greater benefit on disability progression was observed on natalizumab than with fingolimod [Kalincik *et al.* 2015b]. However, a retrospective US claims database analysis suggests that patients receiving fingolimod (n = 185) and natalizumab (n = 185) had a similar reduction of healthcare resource utilization associated with relapses (e.g. hospitalization and/or steroid use) [Bergvall *et al.* 2014a], with no statistical difference in claims-based relapses between the groups (p = 0.8696) [Bergvall *et al.* 2014a]. A German observational cohort study found similar efficacy on relapse rates and disability progression between fingolimod (n = 190) and natalizumab (n = 237). After 12 months of treatment, ARR was 0.06 for natalizumab and 0.10 for fingolimod, with a similar proportion of patients with unchanged and improved EDSS (fingolimod 80.5%; natalizumab 79.3%) [Braune *et al.* 2013]. These findings suggest that fingolimod and natalizumab have similar real-world effectiveness [Bergvall *et al.* 2014a; Braune *et al.* 2013].

An indirect comparison of treatment effects between fingolimod, dimethyl fumarate and teriflunomide using phase III study data has been performed; this analysis was adjusted for differences in patient characteristics and methodologies across the MS trials [Nixon *et al.* 2014]. This modelling approach suggests that fingolimod therapy results in a higher probability of patients achieving NEDA than dimethyl fumarate and teriflunomide therapy; this effect was also observed for a composite measure of clinical efficacy (relapse rates and 3-month CDP) [Nixon *et al.* 2014].

Safety of fingolimod

A cumulative set of data from clinical trials and their extensions, plus postmarketing studies contribute to characterizing the safety profile of fingolimod in patients with RMS [Khatri *et al.* 2011; Vollmer *et al.* 2013; Kappos *et al.* 2014, 2015b; Cohen *et al.* 2015b; Ziemssen *et al.* 2015b]. Common adverse events (AEs) in the placebo-controlled FREEDOMS and FREEDOMS II studies and the FREEDOMS extension study are summarized in Tables 2 and 3, respectively.

In addition to safety data generated from the core phase III studies [Cohen *et al.* 2010; Kappos *et al.* 2010, 2014; Calabresi *et al.* 2014], and their associated extension studies [Khatri *et al.* 2011; Vollmer *et al.* 2013; Kappos *et al.* 2015b], general safety data have been reported from the ongoing LONGTERMS study – the long-term extension study of phase II/III/IIIb trials of fingolimod [Cohen *et al.* 2015b]. Interim, 36-month data from the prospective, long-term PANGAEA study support findings from clinical trials; the most frequent AEs from a safety set of 4001 patients being nasopharyngitis (9.9%), lymphopenia (9.5%), leukopenia (6.1%) and lymphocyte count reduction (5.5%) [Ziemssen *et al.* 2015b].

Table 2. Commonly reported adverse events (occurring in ≥1% of patients and at ≥1% higher frequency with fingolimod 0.5 mg than placebo) phase III FREEDOMS and FREEDOMS II studies, by primary system organ class [Food and Drug Administration, 2015].

	Fingolimod 0.5 mg *n* = 783	Placebo *n* = 773
Infections		
Influenza	11	8
Sinusitis	11	8
Bronchitis	8	5
Herpes zoster	2	1
Tinea versicolor	2	<1
Cardiac disorders		
Bradycardia	3	1
Nervous system disorders		
Headache	25	24
Migraine	6	4
Gastrointestinal disorders		
Nausea	13	12
Diarrhea	13	10
Abdominal pain	11	10
General disorders and administration site conditions		
Asthenia	2	1
Musculoskeletal and connective tissue disorders		
Back pain	10	9
Pain in extremity	10	7
Skin and subcutaneous tissue disorders		
Alopecia	3	2
Actinic keratosis	2	1
Investigations		
Liver transaminase elevations (ALT/GGT/AST)	15	4
Blood triglycerides increased	3	1
Respiratory, thoracic and mediastinal disorders		
Cough	12	11
Dyspnea	9	7
Eye disorders		
Vision blurred	4	2
Vascular disorders		
Hypertension	8	4
Blood and lymphatic system disorders		
Lymphopenia	7	<1
Leukopenia	2	<1
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Skin papilloma	3	2
Basal cell carcinoma	2	1

ALT, alanine aminotransferase; AST, aspartate aminotransferase; FREEDOMS, FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis; GGT, γ-glutamyl transferase; TRANSFORMS, Trial Assessing Injectable Interferon *versus* FTY720 Oral in Relapsing–Remitting Multiple Sclerosis.

Some of the AEs of interest that are associated with fingolimod treatment include cardiac effects following first-dose administration, infections, lymphopenia, liver enzyme elevations, macular edema and fetal risk [Kappos *et al.* 2014]. Key safety events of interest are reviewed.

Table 3. Commonly reported adverse events in the phase III FREEDOMS extension study (extension safety population) [Kappos *et al.* 2015b].

Adverse event (AE) *n* (%)	Continuous fingolimod 0.5 mg ($n = 331$)	Placebo–fingolimod 0.5 mg ($n = 155$)
Any AE	314 (94.9)	148 (95.5)
Infection	240 (72.5)	109 (70.3)
Cardiac disorder	19 (5.7)	10 (6.5)
Abnormally elevated hepatic enzymes	24 (7.3)	20 (12.9)
AE leading to study drug discontinuation	15 (4.5)	14 (9.0)
Most commonly reported AEs*		
Nasopharyngitis	84 (25.4)	44 (28.4)
URT infection	58 (17.5)	24 (15.5)
Lymphopenia	52 (15.7)	17 (11.0)
Headache	41 (12.4)	26 (16.8)
Influenza	33 (10.0)	12 (7.7)
Lymphocyte count decrease	16 (4.8)	14 (9.0)
ALT increase	11 (3.3)	9 (5.8)
SAEs$		
Any SAE	31 (9.4)	11 (7.1)
Hepatobiliary disorders	0	0
Cholelithiasis	0	0
Infections/infestations	8 (2.4)	1 (0.6)
Appendicitis	2 (0.6)	0
Neoplasms‡	7 (2.1)	2 (1.3)
Basal cell carcinoma§	4 (1.2)	0
Uterine leiomyoma	2 (0.6)	0
CNS disorders	6 (1.8)	1 (0.6)
MS relapse	0	0
Epilepsy	2 (0.6)	0
Psychiatric disorders	2 (0.6)	0
Depression	0	0
Other AEs of special interest		
Herpes virus infection	40 (12.1)	14 (9.0)
Sinus bradycardia	1 (0.3)	1 (0.6)
Bradycardia	1 (0.3)	1 (0.6)
Bradyarrhythmia	0	0
Macular edema	1 (0.3)	1 (0.6)

*AEs by preferred term reported in 10% or more of patients in any treatment group during the extension.
$List contains total number of SAEs and lists separately all SAEs reported in at least two patients in any organ system class in any treatment group.
‡Benign, malignant and unspecified (including cysts and polyps).
§Including three SAEs reported after database lock.
ALT, alanine aminotransferase; CNS, central nervous system; ITT, intent to treat; MS, multiple sclerosis; SAE, serious adverse event; URT, upper respiratory tract.

Summary of key label revisions

When fingolimod was approved in 2010 in the USA, there were no contraindications listed [Food and Drug Administration, 2010]. As a result, some patients with cardiac issues, as well as those receiving concomitant medications that could have an adverse effect on the heart, received fingolimod, which led to complications. The US label was revised in 2012, following a review of first-dose observation (FDO) cardiac data, which occurred after a death within the first 24 h after first dose of fingolimod – although there was not any clear evidence that the drug played any role in the death [Food and Drug Administration,

Table 4. US label first-dose monitoring criteria and contraindications for fingolimod 0.5 mg according to the August 2015 label [Food and Drug Administration, 2015].

First-dose monitoring requirements (August 2015)
Observe all patients for bradycardia for at least 6 h after first dose with hourly pulse and blood pressure measurement. Obtain electrocardiogram (ECG) prior to dosing and at end of observation period
Patients who develop heart rate < 45 bpm, second-degree or higher atrioventricular (AV) block, or in whom lowest post-dose heart rate is at the end of the observation period should be monitored until resolution
If symptomatic bradycardia occurs, begin continuous ECG monitoring until resolved. If pharmacological intervention is required, continue this monitoring overnight, and repeat first-dose monitoring for the second dose
Patients at higher risk of symptomatic bradycardia or heart block, or prolonged corrected QT (QTc) interval, or taking drugs with known risk of torsades de pointes should be observed overnight
Contraindications for fingolimod
Patients who in the last 6 months experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization or class III/IV heart failure
History or presence of Mobitz type II second-degree or third-degree AV block or sinus sick syndrome, unless the patient has a functioning pacemaker
Baseline QTc interval ≥ 500 ms
Treatment with class Ia or class III antiarrhythmic drug

2012a]. The list of contraindications included in the label changes that occurred in 2012 (provided in Table 4) allow a clinician to exclude patients with pre-morbid cardiac conditions from receiving fingolimod, thus helping to avoid many of the complications that were of concern before the label change. The label also provided detailed information about first-dose monitoring requirements [Food and Drug Administration, 2012b] to ensure the close monitoring of all patients after treatment initiation with fingolimod. Subsequently, safety information has been updated with data from FREEDOMS II and the postmarketing experience relating to the effects of fingolimod treatment on heart rate and conduction, infections and macular edema [Food and Drug Administration, 2015]. Evidence suggests that diagnosis of neuromyelitis optica (NMO) should be excluded prior to initiation of fingolimod therapy because it may be detrimental in this disease [Min *et al.* 2012; Trebst *et al.* 2014].

Effect of fingolimod on heart rate

Fingolimod has a well-understood, first-dose effect on heart rate and atrioventricular conductivity [Koyrakh *et al.* 2005; Brinkmann *et al.* 2010; DiMarco *et al.* 2014]. This occurs because fingolimod binds and stimulates the S1P receptor subtype 1 ($S1P_1$), which is expressed on myocytes in the atria. Stimulation of $S1P_1$ has a downstream effect, which leads to the slowing of heart rate and conduction [Koyrakh *et al.* 2005; DiMarco *et al.* 2014]. Cardiac effects are transient and mostly asymptomatic owing to the desensitization/internalization of the fingolimod–$S1P_1$ complex [Koyrakh *et al.* 2005; DiMarco *et al.* 2014].

Findings from the phase III clinical trials show that mild to moderate bradycardia events were reported for 0.6% of patients receiving fingolimod 0.5 mg [DiMarco *et al.* 2014; Food and Drug Administration, 2015]. Some patients (7 of 1212) reported symptoms such as dizziness or lightheadedness associated with reduced heart rate, but these were transient and usually did not require treatment [DiMarco *et al.* 2014; Food and Drug Administration, 2015]. Label guidelines detailed in Table 4 specify that all patients should have a baseline and 6 h electrocardiogram (ECG), and their heart rate and blood pressure monitored hourly for at least 6 h after the first dose. Some individuals may have continued bradycardia and require prolonged monitoring and observation until the symptoms have resolved [Food and Drug Administration, 2015], although analysis of the pooled phase III clinical trials revealed the majority of patients (83.0%) were discharged at 6 h whereas 2.6% required extended monitoring on day 2 of FDO [DiMarco *et al.* 2014; Food and Drug Administration, 2015]. There is not thought to be a long-term effect of treatment on heart rate control [Kappos *et al.* 2014]. Holter 24 h ECG

data from FREEDOMS II have shown that second-degree atrioventricular blocks (AVBs) were more commonly reported with fingolimod than placebo on day 1, with Mobitz type 1 AVBs reported in 3.7% of patients receiving fingolimod *versus* 2.0% of those receiving placebo; these were frequently reported within the first 6 h after the first dose [Calabresi *et al.* 2014; DiMarco *et al.* 2014; Food and Drug Administration, 2015].

Information from a range of open-label and post-marketing studies has contributed towards a better understanding of the incidence of cardiac events following the first dose of fingolimod. Interim cardiac findings from the START study–a prospective, 1-week, multicenter, open-label study enrolling up to 7000 patients with RRMS in more than 250 centers in Germany–support the findings from the pivotal clinical studies and show that a small proportion of patients (1%) developed bradycardia (heart rate $<$ 45 bpm) at any time during the post-dose 6-h observation period; 1.6% of patients had a second-degree AVB of Mobitz type I or higher.

A substantial challenge in clinical practice is the effect of concomitant medications on fingolimod first dosing. To tackle this, the open-label, phase IIIb FIRST and the phase IV EPOC studies included patients with RMS who had certain pre-existing cardiac conditions and patients receiving concomitant therapy with drugs to reduce blood pressure or receiving β-blockers or calcium channel blockers [Gold *et al.* 2014; Hughes *et al.* 2014]. Bradycardia AEs were recorded in a total of 15 patients (0.6%) in FIRST and 17 patients (2.2%) in EPOC; most cases were asymptomatic and no patients required treatment. Of note, FIRST revealed that bradycardia was more common among patients with pre-existing heart conditions than those without (1.4% *versus* 0.5%) and among patients receiving concomitant heart medication than those who were not (3.3% *versus* 0.5%) [Gold *et al.* 2014]. First-dose monitoring recommendations for patients who are at higher risk of symptomatic bradycardia or heart block, or prolonged corrected QT interval, or taking drugs with known risk of torsades de pointes require these patients to be observed overnight with continuous ECG in a medical facility [Food and Drug Administration, 2015]. Label contraindications–which relate to pre-existing cardiac conditions–are summarized in Table 4 [Food and Drug Administration, 2015].

Effect of fingolimod on lymphocytes and incidence of infections

Owing to the selective effects of fingolimod on T lymphocytes, immunosurveillance is mostly preserved with fingolimod treatment. Fingolimod sequesters autoreactive central memory T cells in the lymph nodes, preventing their migration into the central nervous system, but spares effector memory T cells to circulate and perform immunosurveillance functions in the peripheral immune system [Mandala *et al.* 2002; Matloubian *et al.* 2004; Mehling *et al.* 2008; Brinkmann *et al.* 2010; Chun and Hartung, 2010; Hla and Brinkmann, 2011]. Fingolimod reduces overall peripheral lymphocyte count by 70%, but this effect is reversible, with counts returning to within the normal range for most patients by 6 weeks after discontinuation and to 80% of pretreatment values by 12 weeks [Francis *et al.* 2014]. Rather than the need for regeneration of the lymphocyte population, this timescale reflects the pharmacokinetic profile of fingolimod, which has an elimination half-life of 6–9 days [David *et al.* 2012; Francis *et al.* 2014].

It is of note that the overall rate of infections (72%) with fingolimod treatment in the FREEDOMS and FREEDOMS II clinical trials was similar to that with placebo. Serious infections were more common with fingolimod (2.3%) than with placebo (1.6%) [Food and Drug Administration, 2015].

The commonly observed reductions in peripheral blood lymphocyte counts are an expected pharmacodynamic outcome of fingolimod therapy, and these actions are thought to be integral to the therapeutic effect of fingolimod in MS [Chun and Hartung, 2010]. In FREEDOMS, analysis of infections by lowest lymphocyte count did not show an increase in fingolimod-treated patients compared with those receiving placebo [Francis *et al.* 2014]. Indeed, similar types of infection were reported between fingolimod and placebo groups in FREEDOMS and FREEDOMS II pooled data, except for influenza (11% *versus* 8%), bronchitis (8% *versus* 5%) and sinusitis (11% *versus* 8%), which were more frequent with fingolimod than placebo, respectively [Food and Drug Administration, 2015].

LONGTERMS data indicate that, compared with the core studies, there is no increased risk of infection AEs with long-term exposure to fingolimod of

greater than 2 years [LONGTERMS cohort incidence rate (IR) 65.8; core study cohort IR 92.0]. For infection serious AEs, the IR was 1.0 for the LONGTERMS cohort compared with 1.1 for the core study cohort [Cohen *et al.* 2015b].

The incidence of herpes zoster infection AEs was low in placebo-controlled studies, albeit higher with fingolimod (2.0%) than placebo (1.0%) [Food and Drug Administration, 2015]. Recent assessment of the risk of varicella zoster virus (VZV) infections from the clinical development program confirm these values, with an incidence of 11 *versus* 6 per 1000 patient years for fingolimod *versus* placebo [Arvin *et al.* 2015]. A similar rate was confirmed in the ongoing extension studies. In the postmarketing settings, the incidence of VZV infection was similar to clinical studies (7 per 1000 patient years) and rates have remained stable over time, suggesting that there is no sign of risk accumulation with prolonged fingolimod exposure [Arvin *et al.* 2015]. However, one fatal case of disseminated varicella zoster has occurred in the postmarketing setting and other serious cases of herpes simplex infections have been reported [Food and Drug Administration, 2015]. Therefore, disseminated herpetic infections should also be included in the differential diagnosis of patients who are receiving fingolimod and who present with an atypical MS relapse or multiorgan failure [Food and Drug Administration, 2015]. US label guidelines also stipulate VZV serology testing and vaccination if a patient is antibody-negative before fingolimod treatment initiation. The latter should be postponed by 1 month should vaccination be required, to allow the full effect of vaccination to establish [Food and Drug Administration, 2015]. Analysis of vaccination response rates in patients with MS on fingolimod treatment showed that most patients can mount immune responses to novel (influenza) and recall (tetanus) antigens, although response rates were reduced in comparison with patients receiving placebo (43% response rate *versus* 75% at 6 weeks post influenza vaccination), and this should be considered by the clinician when vaccinating fingolimod-treated patients [Kappos *et al.* 2015a].

In fingolimod-treated patients, there have been rare cases of cryptococcal meningitis (CM) [Food and Drug Administration, 2015] and progressive multifocal leukoencephalopathy (PML) without prior natalizumab treatment reported in the postmarketing setting [Food and Drug Administration, 2015]. General vigilance for serious infections such as PML is certainly warranted, not only following discontinuation of natalizumab. US label guidelines state that at the first sign or symptom suggestive of PML, fingolimod should be withheld and an appropriate diagnostic evaluation should be conducted. Patients with symptoms and signs consistent with CM should undergo prompt diagnostic evaluation and treatment [Food and Drug Administration, 2015].

The emergence of isolated cases of PML and CM, in the 5 years since fingolimod was launched (approximately 125,000 patients have been treated with fingolimod and total patient exposure now exceeds 240,000 patient years; Novartis, 2015a), suggests that, under rare circumstances, the immune effects of fingolimod may be associated with reduced immune surveillance towards the John Cunningham virus and *Cryptococcus*; these factors need to be further elucidated. The rarity of these infections suggests that fingolimod does not act as a broad immunosuppressant, but vigilance towards signs and symptoms of these serious infections is necessary. CM is a treatable disease, in which early diagnosis and prompt treatment may facilitate full recovery. However, particular attention should be given to those patients with additional risk factors for opportunistic infection, such as advanced age, previous or concomitant use of immunosuppressant drugs and certain other medical conditions.

Concomitant use of fingolimod with antineoplastic, immunosuppressive or immune-modulating therapies or with corticosteroids may increase the risk of immunosuppression [Food and Drug Administration, 2015]. It is therefore of note that label guidelines recommended that, when switching to fingolimod from immune-modulating or immunosuppressive medications, such as natalizumab, teriflunomide or mitoxantrone, the duration of their effects and mode of action should be considered to avoid unintentional additive immunosuppressive effects [Food and Drug Administration, 2015]. Recent studies have focused on the appropriate washout period in patients switching from natalizumab to fingolimod [Cohen *et al.* 2014; Jokubaitis *et al.* 2014; Kappos *et al.* 2015c]. These have recommended 8–12 weeks or even shorter intervals (4–8 weeks) to reduce the likelihood of MRI or clinical disease reactivation, with careful consideration given to the risk of additive effects on the immune system in the first months following treatment

change because of the long elimination half-life of natalizumab [Cohen *et al.* 2014; Jokubaitis *et al.* 2014; Kappos *et al.* 2015c].

For dimethyl fumarate, currently no guidance is provided in the US label regarding switching to other therapies and treatment interruption should be considered if lymphocyte counts less than 0.5×10^9/L persist for more than 6 months [Food and Drug Administration, 2014]. Given that lymphopenia and cases of PML have been reported in patients receiving dimethyl fumarate, vigilance would certainly be warranted when switching to fingolimod to avoid unintended additive immunosuppressive effects.

According to the EPOC study, the absence of a washout period between cessation of the injectable DMT and initiation of fingolimod did not appear to be associated with deleterious additive immune system effects [Fox *et al.* 2014].

There have been case reports of tumefactive MS lesions under fingolimod treatment, some occurring soon after switching to fingolimod therapy [Jander *et al.* 2012; Paul and Bourdette, 2013; Pilz *et al.* 2013; Harirchian *et al.* 2015]. As stated above, clinicians should be mindful of any potential additive immunosuppressant effects of therapies.

Effects of fingolimod on the incidence of macular edema and on pregnancy

Clinical studies have indicated that there is a dose-dependent, low risk of macular edema with fingolimod, occurring in 0.5% of patients (4/783) receiving the 0.5 mg dose in the placebo-controlled studies, predominantly in the first 3–4 months of therapy [Zarbin *et al.* 2013; Food and Drug Administration, 2015]. Initiation of fingolimod in MS has been associated with a modest, relatively rapid increase in macular volume, as assessed by optical coherence tomography over a follow-up period of 5 months [Dinkin and Paul, 2013; Nolan *et al.* 2013]. Label guidelines stipulate that, before treatment, all patients must receive an examination of the fundus including the macular, and at 3–4 months after starting treatment, and again at any time after a patient reports visual disturbances while on fingolimod therapy [Food and Drug Administration, 2015]. According to the label, patients with diabetes mellitus or a history of uveitis are at increased risk of macular edema, so should have regular follow-up examinations [Food and Drug Administration, 2015]. Based on evidence from case reports, the clinician may wish to consider continuation of fingolimod therapy under close monitoring in patients who have stable vision but macular changes. This would potentially enable highly selected patients with MS to continue an effective treatment [Li *et al.* 2014].

Preclinical studies have indicated that fingolimod may cause fetal harm [Food and Drug Administration, 2015]. Therefore, it is specified in the label that women of childbearing potential should use effective contraception during and for 2 months after fingolimod discontinuation, because it takes approximately 2 months to eliminate fingolimod from the body [Food and Drug Administration, 2015]. Of the 66 pregnancies with *in utero* fingolimod exposure in the clinical development program, there were five cases of abnormal fetal development [Karlsson *et al.* 2014]. A fingolimod pregnancy registry has been established to record data on pregnancy outcomes in women exposed to fingolimod should they inadvertently become pregnant.

Historic challenges to fingolimod prescription and ongoing solutions

A major hurdle for clinicians to the prescription of fingolimod has historically been the first-dose monitoring requirements. As detailed in the label, before patients can commence treatment with fingolimod, a range of baseline assessments must be performed, and monitoring is stipulated for at least 6 h after the first dose [Food and Drug Administration, 2015]. These requirements can be challenging to coordinate across the different healthcare specialties and their clinics, and so may have limited the uptake of fingolimod in patients with RRMS.

In the USA, a network of clinics has been established to support first-dose monitoring of fingolimod. The laboratories provide baseline assessments tests, including complete blood counts, liver function tests, varicella serology and ECG. They administer the first dose of fingolimod and run the required first-dose monitoring protocol (see Table 4 for a summary), and complete the appropriate documentation. Independent of these laboratories, an ophthalmologist has to perform an examination of the fundus including the macula before and 3–4 months after fingolimod treatment initiation.

Recently, an in-home first dosing has been introduced, which encompasses the baseline testing and FDO in a nonclinical setting, commonly a patient's own home or setting of their choice. Data from this national program are being collected, but few complications have been reported so far. In the USA there have been more than 800 'service requests' for in-home first dosing since its introduction, which includes FDO and baseline assessments. Thus far, there have been more than 580 in-home FDOs successfully performed and more than 700 physicians have utilized these in-home first-dosing services. This provision makes it easier for the clinician to initiate treatment with fingolimod because it takes the burden off the prescriber for first-dose administration.

Historically, the estimated annual cost of fingolimod, the first oral DMT for MS, has been high relative to the cost of injectable DMTs [Hartung *et al.* 2015] and may have been a barrier to prescription. As the treatment landscape of MS has broadened, with a greater number of therapies now licensed in RMS, other therapies such as dimethyl fumarate now incur a similar cost to fingolimod in the USA (as of December 2013: dimethyl fumarate, $50,573; natalizumab, $51,306; teriflunomide, $45,970; fingolimod, $50,965) [Hartung *et al.* 2015]. In general, the costs of all DMTs for MS in the USA have increased rapidly over the past few years [Hartung *et al.* 2015].

Conclusion

Overall, this review provides a summary of the cumulative dataset from clinical trials and their extensions, plus the postmarketing studies that contribute to characterization of the efficacy and safety profile of fingolimod in patients with RMS. The collective dataset presented here shows that fingolimod has robust effects on clinical and MRI outcomes, which are sustained with continued fingolimod treatment. Significant reductions in BVL are also sustained with long-term treatment. The fingolimod label provides clear guidance for the clinician, particularly in relation to the AEs of interest that are associated with fingolimod treatment, which include cardiac effects following first-dose administration, infections, lymphopenia, macular edema and fetal risk. There have been hurdles to the prescription of fingolimod owing to the first-dose administration requirements, but recent changes such as the development of in-home fingolimod first-dosing processes are helping clinicians to meet these challenges.

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